

**ON THE WEIGHT AND STRUCTURE
OF THE ADRENAL GLANDS AND
THE FACTORS AFFECTING THEM,
IN CHILDREN OF 0-2 YEARS**

By

HILKKA TÄHKÄ

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI,
CHIEF: PROFESSOR ARVO YLPPÖ, M.D., AND FROM THE DEPARTMENT OF
LEGAL MEDICINE OF THE UNIVERSITY OF HELSINKI, CHIEF: PROFESSOR
UNTO UOTILA, M.D.

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PREFACE

The present work was originally suggested to me in 1948 by my esteemed teacher, Professor ARVO YLPPÖ, M.D., Chief of the Children's Clinic. It gives me great pleasure to express my gratitude to him for providing me with the opportunity of carrying out scientific work at the Children's Clinic. The untiring interest shown by him in my work as well as his advice and encouragement have been of very great value to me.

I particularly wish to thank Professor UNTO UOTILA, M.D., Chief of the Department of Legal Medicine, who has not spared himself in guiding my work and on the basis of whose suggestions my work took its final form. Furthermore, I wish to express my gratitude for having been allowed to avail myself of the equipment of the Institute of which he is chief.

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Helsinki, March 1951.

HILKKA TÄHKÄ.

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I. INTRODUCTION

EUSTACHIUS, in 1563, was the first to describe the adrenal glands with certainty, but not until the 18th century is there any evidence in the literature of attempts at elucidating their significance. In the middle of the 19th century adrenal research underwent a decisive change after ADDISON showed that the adrenals are indispensable to the maintenance of life, and described the disease bearing his name. The hundred years that have passed since then have seen an enormous number of investigations into the adrenals, with the purpose of studying their development, structure and function in different situations. By the early 20th century many investigators realised the great importance of the adrenals in the fight of the organism against various harmful factors, e.g. diseases. Basing their results on pathoanatomic findings, several investigators, e.g. THOMAS (1911), GOLDZIEHER (1910), LANDAU (1913), and others advance the opinion that death in acute infectious diseases is due, in the first place, to an insufficiency of adrenals.

The great susceptibility to infections of newborn infants and infants under 6 months has been explained by GOLDZIEHER (1946) as being due to a relative insufficiency of the adrenal cortex, which according to him is present in all children under 6 months. For a great part, he bases these assertions on the changes taking place at this age in the structure of the adrenals. This development of the adrenal cortex, the involution of the foetal cortex and formation of the permanent cortex, have been the subject of keen research. Several theories have been advanced on the significance of the foetal cortex and the factors affecting its involution (GOLDZIEHER 1946, HOWARD 1940, BLACKMAN 1946, etc.), but the problem still remains unsolved. Extensive evidence exists on the anatomic changes

visible in the course of this development (KERN 1911, BENNER 1940, SWINYARD 1943, BLACKMAN 1946, McNEILL 1947).

Recent research has again accentuated the importance of the adrenal cortex. In 1946, SELYE, with his »General Adaptation Syndrome» theory, endeavoured to explain the reactions of the organism to most varied factors with the aid of a uniform mechanism, and one of the most important parts of this mechanism is the adrenal cortex. SELYE (1937, 1946) has shown with extensive animal tests that very varied factors, so-called stresses, produce fairly similar changes in the organism. The fate of the individual in each case is decided by the intensity and duration of the stress in question, and the organism's own resistance, or »adaptation energy». SELYE (1946, 1950), SAYERS & al. (1943—44) and numerous other investigators have found that this resistance of the organism is dependent, primarily, on the pituitary — adrenocortical system. It may depend on the reaction capacity of these organs whether the organism will be able to overcome the detrimental effects of the stress it suffers.

For instance, the above investigators have shown with extensive animal tests that both structural and functional changes are found, at the different stages of the activities of this defence mechanism of the organism, in several important organs, e.g. in the endocrine glands. A fairly great regularity can be shown, with animals, in the changes of the adrenal cortex. The changes e.g. in the size of the adrenal and its lipid content are constant, to such an extent even that a characteristic finding permits far-reaching conclusions regarding the function of the adrenals.

Corresponding investigations, of course, cannot be carried out with man, but there are several points that justify the assumption that the pituitary — adrenocortical system, in the defence mechanism of the human organism too, has a leading function. This has emerged in connection with shock investigations for example (SELYE 1947, MOON 1942, LONG 1947, etc.).

It has been possible, at the convalescent stage of severe infectious diseases of long duration, to demonstrate relative insufficiency of the adrenal cortex (e.g. KAPPERT 1947, adults in and ROMINGER 1948, in children). It therefore seems possible that in cases where the disease was fatal, the infection was severe enough to result in so

considerable adrenal insufficiency that it must be considered as a principal reason for the exitus.

A new stage has again been reached in adrenal research in recent years, with the publication by HENCH, KENDALL & al. in 1949 of their discovery of and results with Cortisone and ACTH. The good results attained with these substances in a very varied range of morbid conditions clarify in a remarkable way the conception of the importance of the anterior lobe of the pituitary and the adrenal cortex in human organism.

The object of the present investigation has been to study the development of the adrenals from autopsy material, and the factors affecting them, and to try so ascertain whether conclusions can be drawn from autopsy findings as to the possible part played by the adrenal cortex in the death of infants.

It is possible to review the immensely extensive literature on the adrenals only in its main features in the following. Further information can be found in the detailed monographs by GOLDZIEHER (1946), HARTMAN & BROWNELL (1949) and SELYE (1950).

II. THE PROBLEM

On the basis of the material collected, the author endeavours to resolve the following problems:

1. The development of the absolute and relative weight of the adrenal glands in the course of the first two years of life and the effect of the birth-weight and sex of the infant on this development.

2. The involution of the foetal cortex and the effect on it of the infant's birth-weight, sex and diseases of varying kind and duration.

3. Changes in the weight of the adrenal glands in accordance with the duration of disease, and variations in such changes in the different diseases.

4. The varying of the lipoid content of the adrenal cortex with children of different ages and in diseases of varying kind and duration.

5. The existence of a law-like regularity in the relationship between the weights of the adrenal glands and the thymus.

6. The existence of a law-like regularity in the relationship between the weights of the adrenal glands and the thyroid gland.

7. The establishing of a possible insufficiency of the adrenal cortex, on the basis of investigations carried out, in some individuals or in certain groups of diseases.

8. The application of the results attained to the »General Adaptation Syndrome».

III. MATERIAL AND METHODS

The present material is collected from autopsies performed at Helsinki University Children's Clinic in 1948—1949. In addition, the author has had the opportunity of performing autopsies on some infants who died immediately after birth, made available by Helsinki University Women's Clinic.

The present material comprises 311 patients from whom the adrenal glands were removed; in 309 instances the thymus was also removed, and in 244 instances even the thyroid gland.

In the following the results are given for infants who died at 0—2 years of age, as the autopsy material of the Children's Clinic comprises so few older children that their grouping would have been practically impossible, and they have therefore been excluded.

Of the patients, 97 were premature and 214 fullterm births.

The breakdown of the present material by age and sex is as shown in Table 1.

Age	Premature births		Fullterm births	
	Male	Female	Male	Female
0— 7 days	19	29	19	9
8—14 »	7	5	5	7
15—30 »	4	3	13	4
1— 2 months	7	6	11	6
2— 3 »	4	3	18	11
3— 4 »	4	3	11	8
4— 5 »	1	1	13	9
5— 6 »	—	—	10	6
6— 9 »	1	—	15	11
9—12 »	—	—	7	5
12—24 »	—	—	6	10
Total	47	50	128	86

Table 1. The patients in the present material, by age and sex.

(The age grouping used in this table is consistent throughout the work. The age group 1—2 months, for instance, includes all the patients who died at the age of 31—60 days.)

By the main cause of death, the present material falls into the following groups (Table 2):

Cause of death	Number of instances
Premature birth	97
Debilitas congenita	2
Laesio cerebri intra partum	9
Vitia congenita cordis	15
Erythroblastosis foetalis	3
Icterus neonatorum gravis (not Rh)	4
Atresia oesophagi (operated)	4
Stenosis hypertrophicans pylori (operated)	2
» » » (not operated)	7
Septicaemia (<i>Pseudomonas aeruginosa</i>)	10
Other septicaemias	4
Meningitis purulenta	4
Pneumonia	27
Gastroenteritis	72
Lues congenita	1
Tuberculosis miliaris et meningeum	9
Encephalitis	2
Leucaemia	3
Diabetes mellitus	2
Idiotia mongoloidea	2
Anencephalus	1
Hydrocephalus (operated)	5
» (not operated)	2
Meningo- or encephalocele (operated)	4
» » » (not operated)	3
Status post laparotomiam	8
Malignant tumour	4
Miscellaneous	5
Total	311

Table 2. Material by diagnosis groups.

The above diagnoses and other relevant data were obtained from the case journals and post mortem records of the Children's Clinic. The author has tried, as a rule, to ascertain the principal disease of the infant and estimate e.g. the duration of the disease accordingly.

The autopsies were carried out within 1—48 hours of the patient's death, the majority within 12—24 hours. The adrenals, thymus and thyroid gland were removed by the author personally in all cases. The endeavour has been to prepare them as accurately as possible, removing the surrounding tissue. The fatty tissue surrounding the adrenal gland has often caused difficulties, as, sometimes, has the separation of a very atrophic thymus from the connective tissue.

Immediately on removal the organs were weighed, to an accuracy in 89 cases of 0.1 g and in 222 cases of 0.01 g. All the weighings were effected by the author personally, using the same weights and scale throughout, found on adjustment to weigh correctly to an accuracy of 1 mg.

After weighing the adrenal glands were cut into sections approx. 5 mm in thickness, which were fixed in 10 % formalin. 5 μ thick*paraffin sections were then taken and stained with *Delafield's* haematoxylin and eosin. From these preparations, the amount of foetal cortex and permanent cortex was estimated by measuring in microscope the thickness of the entire cortex and foetal cortex at a total of 50 points on the sections taken from 4—5 different places in the adrenal glands. Mean values were calculated and the amount of foetal cortex was stated as a percentage of the entire cortex. A determination method of this type, naturally, is fairly uncertain, as a reliable result can only be obtained by volumetric determinations or calculations effected on serial sections. However, the results obtained can be considered indicative of the trend of development. The amount of medulla in the adrenal gland has not been measured as its amount in sections taken from different parts of the adrenal gland varies so much that no clear idea could be obtained using a method like the above. Details connected with the involution of the foetal cortex were observed and examination made for possible adrenal haemorrhages.

The lipid content of the adrenal cortex has been considered as some kind of indicator of its function, as the active hormones of the adrenal gland are steroids (SELYE 1946, 1950, SAYERS & al. 1943—44, etc.). For the determination of lipoids and the so-called ketosteroids, several different methods have been used, e.g. Scarlet-red staining, Liebermann—Burchard—Schultze cholesterol staining, Feulgen's plasmal reaction, Bennett's phenylhydrazine staining, osmic acid staining; furthermore, the preparations were examined in polarized and ultraviolet light. Opinions in the literature on the value of the different determination methods are very contradictory (DEMPSEY & WISLOCKI 1946, DEANE & GREP 1947, KNOUFF, BROWN & SCHNEIDER 1941, ROGERS & WILLIAMS 1947, DUGUID & MILLS 1928, BOSCOTT, MANDL, DANIELLI & SHOPPEE 1948).

Several 5 μ thick frozen sections were taken from all the adrenals in the material. *Scarlet-red* staining was used in every case. A further *Liebermann—Burchard—Schultze* cholesterol staining was carried out in 251 instances, and in 118 instances the sections were inspected unstained in *polarized light*.

The amount of lipid content was estimated by eye and the following grading was employed:

0	=	no lipoids
+	=	lipoid amount scarce
++	=	» » fair
+++	=	» » fairly abundant
++++	=	» » abundant

Efforts have been made to judge the cases as uniformly as possible. In addition, the lipid content of the different zones of the cortex was estimated separately in each case.

In 19 of the present cases, chemical lipid analyses were made for other purposes (Hallman), and these results being available, it has been possible to compare the mutual relationship between the chemical and histological lipid contents. The lipid determinations were effected by the following methods:

Total lipid: by BRUN's method (1939—40)

Cholesterols: by SCHOENHEIMER & SPERRY's method (1934).

Mathematical Review of the Results.

The following formulas have been employed in the calculations:

1. The symbols $x_1, x_2 \dots x_k$ and $y_1 \dots y_l$ denote the quantities measured. Hence,

$$\text{mean value of } x = m_1 = \frac{1}{k} \sum_{i=1}^k x_i,$$

$$\text{mean value of } y = m_2 = \frac{1}{l} \sum_{i=1}^l y_i,$$

$$\text{mean error of the mean value of } x = \sigma(m_1) =$$

$$= \sqrt{\frac{\sum_{i=1}^k (x_i - m_1)^2}{k(k-1)}} = \sqrt{\frac{\frac{1}{k} \sum_{i=1}^k x_i^2 - m_1^2}{k-1}}$$

The probability that m_1 deviates from the true value more than $2 \times \sigma(m)$ is 5 %, more than $2.6 \times \sigma(m)$ 1 %, and more than $3.3 \times \sigma(m)$ 0.1 %. It is assumed here that the quantities studied conform with the so-called normal distribution law, which assumption, in cases like the present, as a rule holds good with sufficient accuracy.

The mean error in the difference of two quantities, m_1 and m_2 , is obtained from the formula

$$\sigma(m_1 - m_2) = \sqrt{\sigma(m_1)^2 + \sigma(m_2)^2}$$

2. The correlation coefficient between the quantities x and y has been computed from the formula

$$r = \frac{m_{12}}{\sqrt{m_{11} \cdot m_{22}}}$$

in which

$$m_{11} = \frac{1}{k} \sum_{i=1}^k x_i^2 - m_1^2, \quad m_{22} = \frac{1}{k} \sum_{i=1}^k y_i^2 - m_2^2, \quad m_{12} = \frac{1}{k} \sum_{i=1}^k x_i y_i - m_1 m_2$$

Here, x_i and y_i , denote the corresponding x and y values, and m_1 and m_2 are the mean values of x and y .

To estimate the significance of the correlation, the quantity

$$t = \sqrt{k-2} \cdot \frac{r}{\sqrt{1-r^2}}$$

is employed.

The probability that the correlation found is significant can be obtained with the aid of t and k from the special table (so-called t -distribution).

3. The angle coefficient of the so-called regression line illustrating the rectilinear dependence of y on x is

$$b_{21} = r \sqrt{\frac{m_{22}}{m_{11}}}$$

In estimating whether b_{21} deviates from the given value β_{21} the following expression can be formed

$$t = \sqrt{\frac{m_{11}}{m_{22}} \cdot \frac{k-2}{1-r^2}} (b_{21} - \beta_{21})$$

upon which a study can be made, with the aid of the t -distribution table, of whether the value obtained differs significantly from zero.

If k is high, $t > 3.3$ corresponds to a 0.1 %, $t > 2.6$ to a 1 % and $t > 2$ to a 5 % probability of error in the conclusion that t deviates significantly from zero.

4. Denominations corresponding to agreed probability of error percentages, p , are often employed as follows:

The difference observed is almost significant, if $1 \% \leq p < 5 \%$

» » » » significant, if $0.1 \% \leq p < 1 \%$

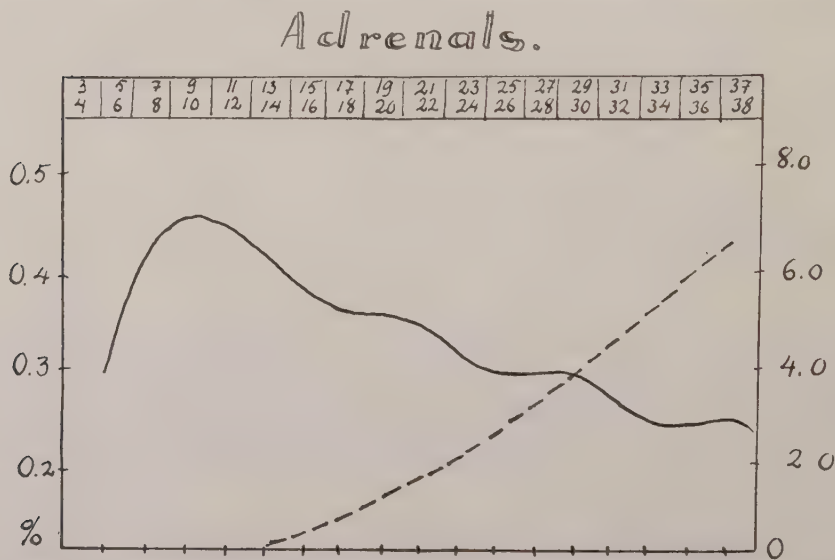
» » » » highly significant, if $p < 0.1 \%$

The above formulas and the more detailed explanations connected with them are advanced e.g. by CRAMÉR 1949.

IV. DEVELOPMENT OF THE WEIGHT OF THE ADRENAL GLANDS

Foetal Period.

The development of the weight of the adrenal glands has been followed from the 3rd—4th months of pregnancy (JACKSON 1909, SCAMMON 1926, EKHOLM & NIEMINEVA 1950). In 1944 CLATWORTHY & ANDERSON published the normal foetal development of the weights of several organs. Their results are based on the values of JACKSON and SCAMMON, and on values collected by JACKSON from the literature. Graph 1 shows the development of the absolute and relative weight



Graph 1. Development of the absolute and relative weight of the adrenals in the foetal period, according to Clatworthy & Anderson.

$$\text{---} = \text{absolute weight, g}$$

— relative weight, %

of the adrenals as given by CLATWORTHY & ANDERSON. The adrenal weights in fetuses of 75—2,500 g, published by EKHOLM & NIEMINEVA from Finland, coincide fairly well with the values given above. Among their results, the adrenal weights in fetuses from the immature stage (birthweight 600—1249 g) onwards are of particular interest in this connection. These values are given in Table 3.

Weight of fetus, g	Absolute weight of adrenal glands, g	Relative weight of adrenal glands	Number of instances
600—1249	2.4—3.7	1: 281 or 0.35 %	14
1250—2500	3.5—4.78	1: 94 or 0.25 %	16

Table 3. Adrenal weights, according to EKHOLM & NIEMINEVA, of fetuses of 600—2,500 g in weight.

According to BENNER, the weight of adrenal glands is proportionate to the length of the fetus. She gives the following mean values:

Length of fetus, cm	Weight of adrenals, g
25—30	3.8
31—35	3.3
36—40	4.0
41—45	5.7
46—50	6.4
51—55	10.3

SWINYARD has measured the volume of the adrenal glands with negroes, from a 3½-month fetus up to 17 years of age. He found that the adrenal cortex grows greatly towards the very end of pregnancy.

Postnatal Development of the Weight of the Adrenal Glands.

Table 4 gives the average weights of adrenal glands in fullterm newborn infants reported by the different researchers.

According to SCAMMON, the weight of the adrenal gland drops during the first two weeks of life by approx. 1/3 of the birth weight, and by about a half by the age of three months.

The following shows the average weights of the adrenal glands in various age groups as reported by certain researchers. The results are mean values from miscellaneous autopsic materials.

	Absolute weight of adrenal glands, g			Relative weight of adrenal glands, %		
		male	female		male	female
BENNER (1940)	6.4					
CASTALDI & VANNUCCI (1941)		9.01	7.19			
CLATWORTHY & ANDERSON (1944)	7.0			0.22		
ELLIOT & ARMOUR (1911)	4.6					
HASNER (1949)	4.9			0.24		
JACKSON (1909)						
SCAMMON (1926)	7—8					
SCHEEL (1908)	4.85	4.7	5.0			
SCHILF (1922)	6.83	7.37	6.39			
STARKEL & WĘGRZYNOWSKI (1910) ...	6.2					
UOTILA (1940)		6.93	6.96		0.207	0.212

Table 4. Average weights of adrenal glands with fullterm newborn infants.

BENNER:

Age	Weight of the adrenal glands, g	Number of instances
Newborn	6.4	44
2 days	4—10	64
3 days—1 month	4—5	33
2—12 months	4—5	32
1—2 years	4.7	44

CASTALDI & VANNUCCI:

Age	Weight of the adrenal glands, g	
	male	female
8—9 foetal months	3.44	3.45
newborn	9.01	7.19
0—3 months	4.63	3.12
4—6 »	3.43	2.29
7—12 »	4.34	3.74
1—2 years	4.84	4.84

SCHILF:

Age	Weight of the adrenal glands, g	
	male	female
Premature infants	2.91	3.99
newborn	7.37	6.30
1 month	3.69	2.84
2 months	3.00	2.63
3 »	2.54	3.03
4 »	2.85	2.61
5 »	2.30	2.10
6 »	1.69	—
7—12 »	2.74	2.74
1 year	2.97	2.76
2 years	3.52	3.25

STARKEL & WĘGRZYŃSKI: 100 instances 0—5 years

Age	Weight of t adrenal glands, g
Stillbirths and premature births	6.2
0—7 days	5.0
7 days—1 month	4.0
1—2 months	3.0
2—6 »	2.9
6—12 »	3.2
1—1½ years	3.1
1½—2 »	3.1
2—3 »	4.9
3—4 »	4.0
4—5 »	6.0

HASNER:

Age	Weight of the adrenal glands, g
Newborn	4.9
6 months	2.8
12 »	3.1
2 years	3.3

UOTILA:

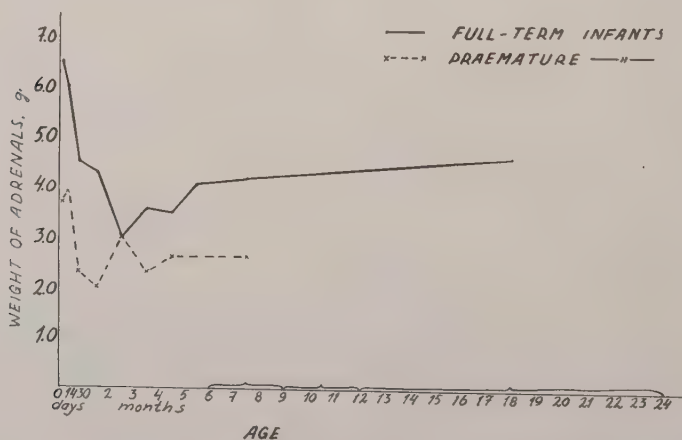
Age	Weight of adrenal glands, g		Number of instances	
	male	female	male	female
Newborn	6.9	7.0	88	76
0—6 months.....	4.4	6.6	7	7
7—12 »	6.2	4.0	5	1
1 year	4.5	6.3	4	3

The weight of the adrenal glands of premature infants, given separately, has not been found in the literature. BENNER states, without specifying the instances, that the development of the weight of the adrenal glands of premature infants is similar to that of fullterm infants.

Present Investigations

Fullterm Infants.

Graph 2 shows the average weights of the adrenals for the full-term infants of the present material, by the different age groups. Table 5 gives the same figures as accurate values.



Graph 2. Development of the adrenals according to age: fullterm infants and premature births.

Age	Weight of adrenals, g		Number of instances
	Mean value	Range	
0—7 days	6.50 ± 0.37	3.05—12.00	28
8—14 »	6.11 ± 0.45	4.40—9.85	13
15—30 »	4.52 ± 0.31	2.00—6.60	16
1—2 months ...	4.30 ± 0.36	1.63—8.25	17
2—3 » ...	3.51 ± 0.22	1.71—6.50	29
3—4 » ...	4.10 ± 0.28	2.50—6.80	19
4—5 » ...	4.03 ± 0.30	2.30—7.90	22
5—6 » ...	4.64 ± 0.27	2.58—6.57	16
6—9 » ...	4.69 ± 0.24	2.78—7.10	26
9—12 » ...	4.67 ± 0.39	2.07—7.12	12
12—24 » ...	5.23 ± 0.39	3.54—8.15	16

Table 5. Weight of the adrenals by the different age groups.

It can be seen from the above that there is scarcely any change at all in the weight of the adrenals during the first 14 days. In the 15—30-day age group there was a distinct drop, from $6.50 \rightarrow 4.52$ g. The mean error in the difference between the mean values of the adrenal weights of the 0—7-day and 15—30-day age groups is ± 0.48 . The established reduction in weight is equal to 4.1 times the above mean error; hence the result is statistically highly significant. The average weight of the adrenals of infants of 15—30 days is 69 % of that of infants of 0—7 days.

Further it is seen that the adrenal weight drops continuously, attaining its lowest value, 3.51 g, at the age of 2—3 months. This figure is approx. 54 % of the adrenal weight of infants of 0—7 days. From the age of 3 months the weight of the adrenals begins to increase slowly, and the increase continues throughout the material; with infants of 12—24 months the average weight of the adrenals is 5.23 g i.e. still distinctly below the value at birth. Calculus of correlation show that the increase in the adrenal weight from the age of 3 months $\rightarrow$ 24 months is highly significant.

Premature Births.

The development of adrenal weight with premature births is shown in Graph 2 and Table 6.

Age	Weight of the adrenals, g		Number of instances
	Average	Range	
0—7 days	3.77 ± 0.19	1.02—6.40	48
8—14 »	3.81 ± 0.32	2.50—5.70	12
15—30 »	2.68 ± 0.47	1.40—4.80	7
1—2 months ...	2.00 ± 0.14	1.60—2.90	13
2—3 » ...	3.51 ± 0.32	2.30—4.88	7
3—4 » ...	2.75 ± 0.35	1.63—4.00	7
4—5 » ...	3.22	2.90—3.55	2
5—6 » ...	—	—	—
6—9 » ...	3.07	—	1

Table 6. Weight of the adrenals in the different age groups of premature births.

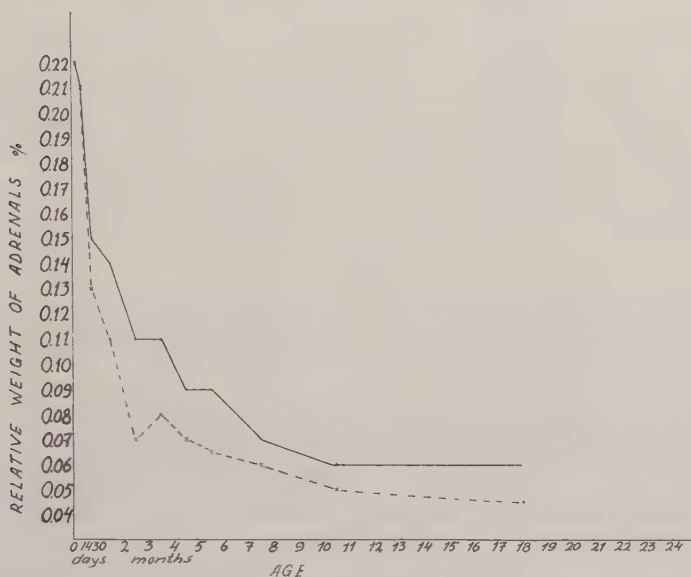
Graph 2 and Table 6 show that the weight of the adrenals, with premature births as well, remains practically constant up to the age of 14 days, upon which it begins to decrease. In the 15—30-days group the weight has fallen to 2.68, 71 % of the adrenal weight of the 0—7-day age group. The minimum value is already attained in the age group 1—2 months, when the adrenal weight is 2.00 g, or approx. 53 % of the initial value. In the following age groups the adrenal weight rises again, but no distinct law-like regularity can be discerned, the instances being too few in these older age groups.

Development of the Relative Weight of the Adrenals.

In observation of the development of the size of the different organs in the foetal period valuable help in judging the matter can be obtained from the relative weights of the organs in question, i.e. their weights compared with the body weight of the relevant foetus. The value of the relative weights is considerably reduced, in the postfoetal period, resulting from the fact that in the course of a disease an infant's nutritional condition, generally, deteriorates. Diseases of different kind and duration are very varying in effect in this respect. The relative values calculated from the established weight at death, therefore, are not comparable. To clarify the matter, a so-called ideal weight has been worked out for the patients of the material, employing

the generally accepted formula: birth weight + age in months $\times$ 600 g (SIMMONS & TODD 1938). The relative weights of the organs, also, in each individual case, have been calculated from this ideal weight. The values obtained in this way, admittedly, cannot be considered as normal results, as the ideal weights of the adrenals are not known.

Graph 3 shows the relative weight of the adrenals in fullterm infants, calculated from the established weight at death and from the estimated ideal weight. Both graphs have a distinctly declining



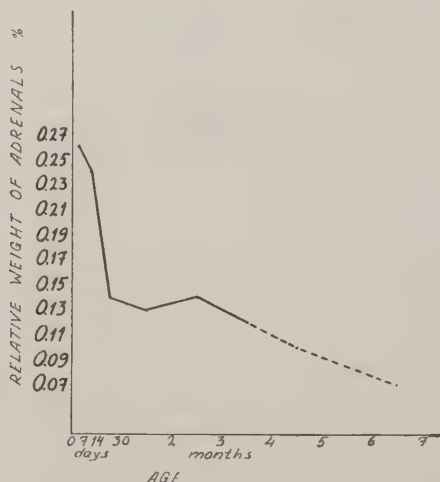
Graph 3. Development according to age of the relative weight of the adrenals: fullterm births.

————— = calculated from the established weight at death
 - - - - - = calculated from the estimated ideal weight.

course, which in fact is natural, when the rapid growth of infants at this age is taken into consideration. Apart from the newborn infants (age at death under 15 days), the relative weights calculated from the ideal weight are distinctly lower than the values calculated from the weight at death.

Graph 4 shows the development of the relative weight of the adrenals in premature births. It has not been possible to work out

an ideal weight for this group as the development of the weight of premature births does not conform so distinctly to rule as does that of fullterm births.



Graph 4. Development of the relative weight of the adrenals with premature births.

A comparison of the graphs showing the relative weights of full-term infants (calculated from the weight at death) and of premature births indicates that for premature babies the initial values are slightly higher than for fullterm births, but that from the 15—30-day age group onwards no distinct differences can be observed in the results.

Relationship of Birth Weight to the Weight of the Adrenals.

The fact that the adrenals have been found to grow considerably towards the very end of pregnancy (JACKSON 1909, SCAMMON, SWINYARD 1943, etc.), justifies a study of whether any correlation can be established in the present material between the birth weight of the infant and the adrenal weight ascertained. In Table 7 each group includes only infants who died within 24 hours of birth, thus excluding the influence of various external factors on the size of the adrenals.

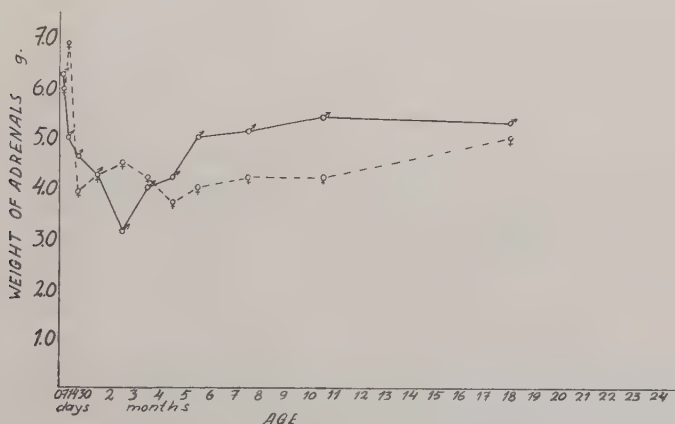
Birth weight, g	Average weight of adrenals		Number of instances
	Absolute g	Relative %	
800—1249	2.89 ± 0.58	0.29	6
1250—1999	4.66 ± 0.53	0.28	4
2000—2499	4.31 ± 0.57	0.20	4
over 2500	6.23 ± 0.48	0.23	4

Table 7. Relationship between birth weight and adrenal weight.

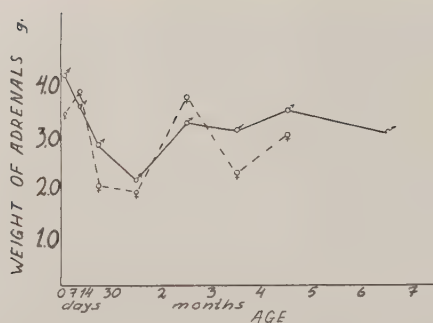
Although the instances are so few, it is obvious from Table 7, that the absolute weight of the adrenals increases considerably towards the end of the pregnancy, whereas the relative weight declines, probably due to the fact that the weight of the child, as is known, greatly increases in the last weeks of pregnancy.

Weight of the Adrenals in Female and Male Infants.

The average weights of the adrenals, separately for girls and boys, are shown, for fullterm births in Graph 5, and for premature births in Graph 6.



Graph 5. Development according to age of the weight of the adrenals in different sexes: fullterm births.



Graph 6. Development according to age of the weight of the adrenals in different sexes: premature births.

It can be concluded from these that no distinct difference between the adrenal weights of the different sexes can be found. The differences in the older age groups of Graph 5 have no statistical significance.

Review of Results.

A review of the above results on the development of the weight of the adrenals shows that the trend of development coincides fairly well with the findings of other researchers (SCAMMON, SCHILF, STARKEL & WĘGRZYŃOWSKI). One difference, however, is that in the present material the average weight of the adrenals declines from 0→3 months and then starts to increase slowly, whereas in SCHILF's and in STARKEL & WĘGRZYŃOWSKI's material the decline in the weight of the adrenals continues up to 6 months. In addition, the absolute weights of the adrenals in the present material are somewhat higher than those found by the above researchers. These differences are probably due to difference in material, for the results of all the researchers are based on miscellaneous autopsic materials. SELYE (1937, 1946, 1950) and many others have shown that diseases and other stresses rapidly affect the size of the adrenals, and that the effect of stresses of different kinds and duration is varying. No normal material proper is available for comparison, accidental death being very rare at this age. — Another possibility to be considered is that in some cases the fairly great weight of the adrenals may be due to the fact that, in spite of attempts to

do so, it has been impossible entirely to remove the fat surrounding the adrenals.

The absolute weights of the adrenals are lower with premature births than with fullterm infants, but the trend of development is similar. With premature births, it is true, the postnatal reduction in size seems to be somewhat more rapid than with fullterm infants. The relative weights, on the other hand, are higher in premature births in the first two weeks of life, while no distinct difference can be shown later on.

The considerable growth of the adrenals towards the end of the pregnancy is also evident from this material, and the values obtained coincide fairly well with published results, e.g. CASTALDI & VANNUCCI, SCHILF, and EKHOLM & NIEMINEVA.

In CASTALDI & VANNUCCI's material the adrenals of female infants, generally, are somewhat smaller than those of male infants. The other researchers have not established this difference, nor has any difference between the sexes been found in the present material.

To summarise the results it can be said that:

1. *With fullterm infants the absolute weight of the adrenals decreases up to the age of 3 months, representing at that point 54 % of the newborn value. The weight then begins to rise, and the rise continues throughout the material. At 2 years still the adrenal has not attained the weight at birth.*
2. *With premature births the adrenals decrease similarly but at a greater rate; the lowest value is found in the 1—2-month age group, representing approx. 53 % of the weight at birth.*
3. *The relative weight of the adrenals decreases throughout the material. Development is fairly identical with fullterm and premature births.*
4. *The adrenals grow considerably towards the end of pregnancy.*
5. *No difference is found in the adrenal weight of male and female infants.*

V. FOETAL CORTEX.

The considerable decrease of the adrenals in the first few months of life is possibly due, to a great extent, to the involution of the so-called foetal cortex.

In the adrenal cortex of a newborn can be distinguished: a light-coloured, narrow exterior part and a large, sanguineous interior part. This observation was first published by STARKEL & WEGRZYŃSKI (1910), and about simultaneously by THOMAS (1911).

The light-coloured exterior layer is the so-called permanent cortex, and the dark interior part the so-called foetal cortex (HETT 1925, SWINYARD, BENNER etc.).

SWINYARD has measured separately the volumes of the permanent cortex and foetal cortex during and after the foetal period. He found that the considerable growth of the adrenals towards the termination of pregnancy is due to the immense growth of the foetal cortex at that time. According to SWINYARD, the foetal cortex constitutes approx. 85 % of the entire cortex of the newborn. HETT and KEENE & HEWER (1927) have assessed the amount of foetal cortex at approx. 65—75 % of the entire cortex, and ELLIOT & ARMOUR at approx. 80 %.

Immediately after birth with the foetal cortex beginning to degenerate, considerable changes occur in the adrenal cortex (LANDAU, ELLIOTT & ARMOUR GOLDZIEHER 1946). KEENE & HEWER, however, maintain that the degeneration of the foetal cortex can be observed within the last ten weeks of pregnancy.

In 1911 the involution of the foetal cortex was described in detail for the first time by KERN. His work still constitutes the basis of subsequent research, and will be reviewed in the main below. KERN distinguishes four stages in the postfoetal development of the adrenal cortex:

- I The stage of hyperaemia: From newborn to 1 month. The limits of the different parts of the cortex are still not quite distinguishable. Zona glomerulosa can be roughly distinguished from the interior part, which is hyperaemic, and in which some cellular degeneration is present.
- II The stage of complete degeneration: Approx. 1—12 months. Zona glomerulosa, fasciculata and reticularis develop into the exterior part. The interior part displays hyperaemia, largedrop adiposis, phagocytosis, pigmentation, and increase of connective tissue.
- III Medullary capsule formation: Approx. 1 year. The degenerated cells and hyperaemia disappear, and what remains is a thick capsule of connective tissue surrounding the medulla.
- IV 1 year to puberty: The connective tissue capsule surrounding the medulla disappears, and the cortex and medulla grow contiguous.

GOLDZIEHER, BENNER, and McNEILL have shown that the degeneration of the foetal cortex starts in its median parts, including the whole foetal cortex by the second week of life. According to McNEILL, the foetal cortex proper has disappeared by the end of the third week. BENNER states that the connective tissue remaining from it begins to decrease rapidly at the age of 2 months, and with children of 5—6 months only a thin connective tissue capsule is found, which disappears at the age of 2—3 years. According to SWINYARD's volume measurements, this connective tissue capsule constitutes, in a child of 1 year, 15.9 % of the entire adrenal. In the course of the second year of life it gradually disappears.

The involution of the foetal cortex of premature babies takes place in the same way as that of fullterm babies (LEWIS & PAPPENHEIMER 1916, SWINYARD, BENNER).

At the same time as the foetal cortex is involuted a permanent cortex grows in its stead. According to Benner, the permanent cortex is doubled by the third week of life, and tripled by the end of the first month of life. From the third week onwards, zona glomerulosa and zona fasciculata can already be distinguished. Similar results have also been attained by KEENE & HEWER, SWINYARD, and McNEILL. According to KEENE & HEWER, zona reticularis begins to develop at the age of

approx. 3 months. BLACKMAN, again, maintains that its beginning is already observable in the first postnatal week.

SWINYARD, BENNER, and BLACKMAN have shown that growth can be observed in the adrenal cortex throughout childhood up to puberty.

SWINYARD has also investigated the size of medulla by volumetric determinations. With the newborn there is little medulla, the ratio cortex: medulla being 214.7: 1. Medulla also grows throughout infancy, and at the age of 1 year the above ratio is 15.2: 1.

According to GOLDZIEHER (1946), the prenatal large foetal cortex is due to the relatively anoxic condition of the foetus. This opinion is based e.g. on the finding that the involution of the foetal cortex is retarded in cyanotic children who have died of congenital heart malformations.

On the other hand BLACKMAN, HOWARD, etc. are of the opinion that the foetal cortex is androgenic in its function. This assumption is supported by the observation that a larger than normal foetal cortex has often been encountered in connection with the adrenogenital syndrome (DIJKHUIZEN & BEHR 1940, BLACKMAN, CARLGREN 1949, etc.).

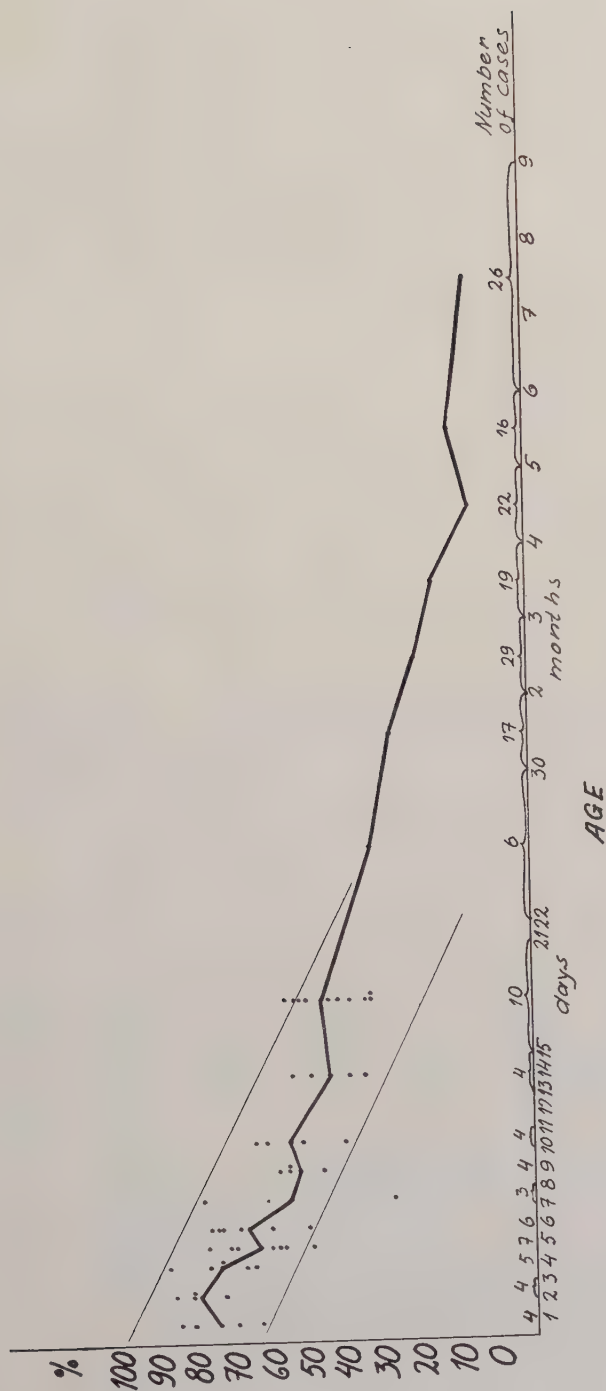
Furthermore, in some other diseases, changes have been found in the regular involution of the foetal cortex. These matters will be dealt with in greater detail later.

Present Investigations

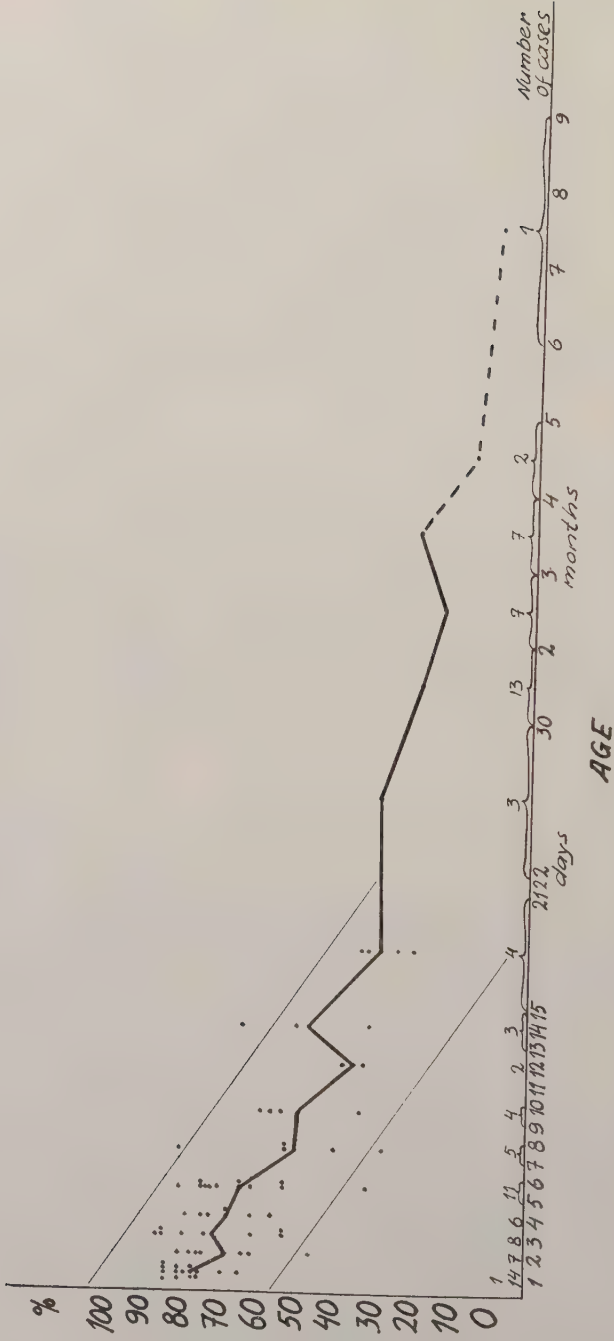
Graphs 7 and 8 show the development of the foetal cortex in full-term and in premature babies. Up to the age of 21 days the mean value curve of the foetal cortex falls fairly evenly, although fluctuations in individual cases are considerable. Calculus of correlation show that no difference can be ascertained mathematically in the involution of the foetal cortex between fullterm and premature infants.

Table 8 shows that the development of the foetal cortex with premature infants in the different weight classes is identical; hence, the degree of prematurity does not affect the development.

The involution of the foetal cortex continues after 21 days of age, though less uniformly. At this age its histological picture begins to change distinctly. A distinct foetal cortex, with cells at different



Graph 7. Development of the foetal cortex with fullterm infants, indicates the normal range of variation to an accuracy of 1 %.



Graph 8. Development of the foetal cortex with premature births, indicates the normal range of variation, to an accuracy of 1 %.

Age	Birth weight 800—1249 g		Birth weight 1250—1999 g		Birth weight 2000—2499 g	
	Average foetal cortex %	Number of cases	Average f.c. %	Number of cases	Average f.c. %	Number of cases
1 day	79	6	78	4	75	4
2 days	73	3	54	2	74	2
3 »	69	2	74	6	—	—
4 »	—	—	68	5	67	1
5—6 »	73	1	62	4	64	6
7—8 »	—	—	51	5	—	—
9—10 »	—	—	57	2	43	2
11—12 »	—	—	33	1	37	1
13—14 »	—	—	47	2	50	1
15—21 »	31	1	28	2	20	1
22—30 »	—	—	28	1	29	2
1—2 months	20	1	20	7	18	5
2—3 »	—	—	13	3	15	4
3—4 »	—	—	14	4	27	3
4—5 »	—	—	6	1	8	1
5—6 »	—	—	—	—	—	—
6—9 »	—	—	0	1	—	—

Table 8. The development of foetal cortex in premature infants of various weights.

stages of degeneration and, in the majority of cases, hyperaemia and some connective tissue, has been found with all infants under 21 days.

From 21 days up to approx. 2—3 months a fair abundance of connective tissue, as a rule, is encountered as a residue of the foetal cortex, and in the connective tissue varying amounts of degenerating cells and hyperaemia. From the age of 3 months onwards, apart from a few exceptions, only a connective tissue capsule surrounding the medulla can usually be found. Already from 4 months onwards there have been some patients in which this connective tissue capsule has been so thin that it cannot be measured. Generally, the connective tissue capsule has been found in all children under one year and in the majority of the those older than 1 year.

According to GOLDZIEHER (1946), retardation of foetal cortex involution can be expected in connection with anoxia. Hence, a larger

than normal foetal cortex should be found in patients who have died of diseases in which respiratory difficulties and cyanosis were present. The most important among such diseases would be: premature birth, pneumonia, cerebral haemorrhages and congenital heart malformations. Graphs 7 and 8 and Table 8 show that premature birth as such has no effect. Tables 9 and 10 specify the cases in which the foetal cortex is considerably above the so-called normal range of variation, while Tables 11 and 12 show the instances in which the foetal cortex is smaller than normal. Tables 9 and 10 include no patients that died expressly of the above diseases. Nor can it be shown that the instances given in Tables 9 and 10 and in Tables 11 and 12 possess any essential differences as regards diagnosis, age, duration of disease or adrenal weight of the patients. Neither does the varying duration

Case No	Diagnosis	Age	Duration of disease	Weight of adrenals, g	Foetal cortex %	Average f.c. % at same age
254/48	Pneumonia	21 days	21 days	3.60	69	42
26/49	Icterus neonatorum gravis ...	21 »	21 »	4.98	56	42
256/48	Septicaemia	28 »	18 »	4.5	49	32
40/49	Haematoma subdurale	1½ months	1½ months	8.25	56	23
159/49	Vitium cordis cong.	1½ »	1½ »	3.99	50	23
369/48	Stenosis hypertr. pylori	2 »	2 »	4.3	34	18
94/49	Encephalocele ...	2 »	2 »	2.54	42	18
251/48	Tumor hepatis ...	2½ »	2 »	6.5	36	18
285/48	Gastroenteritis ...	3 »	1 »	4.0	32	15
407/48	»	3 »	1 »	6.00	35	15
224/49	Vitium cordis cong.	3 »	3 »	3.52	37	15
229/48	Gastroenteritis ...	3½ »	8 days	5.7	27	10
399/48	Vitium cordis cong.	4 »	4 months	3.32	30	8
409/48	Lues cong.	4 »	4 »	4.08	23	8
135/49	Pneumonia	5 »	8 days	6.57	20	6
362/48	Stenosis hypertr. pylori	5 »	4½ months	4.4	20	6
148/49	Gastroenteritis ...	6 »	4 days	6.35	20	5

Table 9. Fullterm infants in which the foetal cortex % is considerably higher than the average value.

Case No	Diagnosis	Age	Weight of adrenals, g	Foetal cortex %	Average foetal cortex % at same age
108/49	Præmaturus	8 days	5.62	80	55
3/49	»	14 »	3.14	64	32
239/48	»	1 $\frac{1}{2}$ months	2.2	49	19

Table 10. Premature infants in which the foetal cortex % is considerably higher than the average value.

Case No	Diagnosis	Age	Duration of disease	Weight of adrenals	Foetal cortex %	Average f.c. % at same age
105/49	Septicaemia	5 days	1 day	4.98	48	63
415/48	Laesio cerebri intra part.	7 »	7 days	3.05	27	55
146/49	Vitium cordis cong	28 »	28 »	3.52	13	32
188/49	Meningomyelocele lumb.	1 month	1 month	3.22	12	26
57/49	Idiotia mongoloidea	2 $\frac{1}{2}$ months	2 $\frac{1}{2}$ months	1.78	5	19

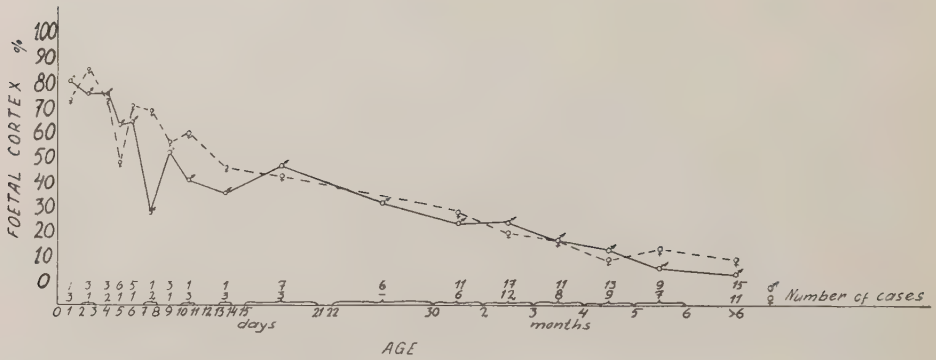
Table 11. Fullterm infants in which the foetal cortex % is considerably lower than the average value.

Case No	Diagnosis	Age	Weight of adrenals, g	Foetal cortex %	Average foetal cortex % at same age
92/49	Praematurus	2 days	3.88	45	75
144/49	»	6 »	5.82	32	63
102/49	»	8 »	4.75	27	55

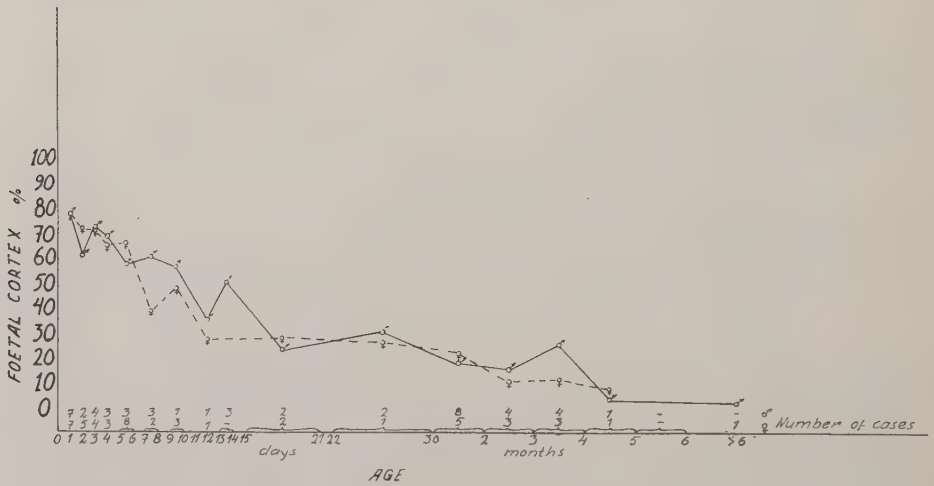
Table 12. Premature infants in which the foetal cortex % is considerably lower than the average value.

of the diseases affect the involution of the foetal adrenal cortex within the normal range of variation.

Graphs 9 and 10 show that no difference can be found between male and female infants in the development of the foetal cortex.



Graph 9. Development of the foetal cortex with different sexes: fullterm infants.



Graph 10. Development of the foetal cortex with different sexes: premature births.

Comparison of the involution of the foetal cortex with reduction in the adrenal weight in the first few months of life shows that although the foetal cortex is considerably reduced within the first two weeks there is no change worth mentioning in the weight of the adrenals (Graph 2). The explanation is possibly that the development of the permanent cortex at this stage is capable of preventing the decrease of the organ, in spite of the degeneration of the foetal cortex. Later on,

with the more complete involution of the foetal cortex, the new-formed permanent cortex can no longer prevent a reduction in the weight of the organ. The histological changes found with the patients of the present material at the different stages of the involution of the adrenal foetal cortex are very similar to those described by other researchers (KERN, BENNER, McNEILL, etc.).

The attention is attracted particularly by the fact that the development of the size of the foetal cortex, and of the adrenal, is similar with fullterm and premature births, although it has been shown that it is towards the end of pregnancy that the adrenal and especially its foetal cortex grow considerably. It would therefore seem that the transition from intrauterine to the extrauterine condition has a decisive effect on the development of the adrenal cortex. This effect even seems to be independent of the degree of prematurity (Table 8). This phenomenon could be explained as being due to hormonal factors, e.g. the exclusion of the effect of the mother's hormones, in this case primarily ACTH, after birth.

In addition, it appears that the development of the foetal cortex is not dependent to any great degree on the various diseases of the infants, but does seem to bear correlation to their age. — Regarding the theory of the androgenic nature of the foetal cortex of the adrenal, no conclusion can be drawn on the basis of the investigations carried out.

To summarise the development of the foetal cortex, it can be said that:

1. *The foetal cortex decreases fairly rectilinearly up to the age of 21 days, although individual variations may be considerable. Its decrease continues subsequently, but is no longer as regular.*

2. *Development with fullterm and premature infants is similar.*

3. *Histological changes present in the foetal cortex: to start with, degenerating cells, hyperaemia, later increased connective tissue content, and, from approx. 2—3 months to 1—2 years, a layer of connective tissue surrounding the medulla is found.*

4. *The kind and duration of disease suffered by the patients does not seem to affect the development of the foetal cortex.*

5. *The development of the foetal cortex is identical with male and female infants.*

VI. ON THE EFFECT OF DIFFERENT FACTORS ON THE ADRENALS

SELYE (1946, 1950) has shown that the adrenal cortex reacts very readily to all kinds of stimuli. This is manifested in functional variations of the cortex, and is also reflected in the size and lipoid content of the adrenals. Changes in the size and lipoid content of the adrenals usually enter at the same time, and hence it may be advisable to deal with these points together. The adrenal findings caused by different stimuli are varying, being decisively affected in each case by the type of the stimulus in question, its intensity and duration, and the organism's own reaction capacity (SELYE 1946, SAYERS & SAYERS 1948, etc.). This explains why the results published in the literature differ and are often contradictory. Certain examples are given in the following.

SCHILF has found that the average adrenal weight with soldiers was 14.0 g, and with other adult males 11.7 g. He considers this due to the soldiers having been exposed to continued strain. A similar explanation is offered by ROGERS & RICHTER (1948) for the fact that the same rat strain when wild has larger adrenals than when living in captivity.

In 1906 ELLIOT & TUCKET found in animal tests that the adrenal cortex contained plenty of lipoids while the animal was at rest; in connection with some stress they were reduced.

Several investigators explain the disappearance of lipoids by increased activity of the adrenal cortex, and the storage of lipoids while the organ is at rest (SELYE 1946, SAYERS & al. 1943—44, SAYERS & SAYERS 1948, DOSNE & DALTON 1941, etc.). FLEXNER & GROLLMAN (1939), again, maintain the contrary.

With low atmospheric pressure tests, ARMSTRONG & HEIM (1938), GOLDZIEHER (1946), HAILMAN (1944), DARROW & SARASON (1944), etc., found that anoxia causes adrenal hypertrophy and a reduction in lipid content.

KARWICKA (1911), KOLMER (1918), and LEWIS & PAPPENHEIMER are of the opinion that nutritional condition in no way affects the size and structure of the adrenals.

On the other hand, JACKSON (1915) has shown with rats that acute hunger causes an increase in the absolute and relative weight of the adrenals, whereas in chronic hunger the absolute weight is reduced and the relative increased. ELLIOT & TUCKET and SARASON (1943) observed that with acute hunger large adrenals poor in lipoids were found in the test animals. MULINOS & POMERANTZ (1941) have found atrophy of the adrenals in chronic malnutrition. The same was found by SELYE (1950), keeping test animals on a diet poor in proteins. SAYERS (1950) has come to the same conclusion.

According to SELYE (1946, 1950), the defence mechanism of the organism reacts to the greatest variety of noxious factors in the same way, in accordance with the principles of the so-called »General Adaptation Syndrome» (GAS). During the first stage of the GAS, the alarm reaction, when the defence mechanism of the organism begins to function, the adrenals grow larger and poor in lipoids, especially cholesterol. In the second, the stage of resistance, the adrenals remain large but the lipid content returns practically to normal. In the third, the stage of exhaustion, in which the defence mechanism of the organism is broken down, the adrenals are again large and poor in lipoids.

In animal tests, SELYE (1937, 1946) elicited the GAS e.g. by muscular strain, thermic stimuli, poisons, infections, etc. DOSNE & DALTON found similar adrenal changes in connection with exposure to cold, and DEANE & McKIBBON (1946) and DEANE & SHAW (1947) in lack of pantothenic acid.

The above contradictory results of adrenal changes elicited by hunger are explained by SELYE (1950) with the aid of the GAS as follows: Acute hunger causes an alarm reaction when the adrenals are large and poor in lipoids. In chronic hunger, again, the animals are at the stage of resistance, and the adrenals are rich in lipoids. A greatly prolonged state of hunger causes complete exhaustion when

the adrenals are free of lipoids, and necroses and haemorrhages are often found. Similar results have been achieved by UEHLINGER (1948) with human material.

SELYE emphasises the importance of the adrenocorticotrophic hormone of the anterior pituitary (ACTH) as the regulator of the adrenal functions. SAYERS & al. (1943—44), and SAYERS & SAYERS (1948), in extensive investigations, have followed the influence of ACTH and the different stresses on the size and lipoid content of the adrenals. The instances are divided into 6 different groups as follows:

»Type 1. *Sudden temporary period of stress.* In this situation there is a sudden temporary increased demand for cortical hormones resulting in a temporary increase in pituitary adrenocorticotrophic activity. The sudanophilic substance, the cholesterol and the ascorbic acid undergo rapid depletion, following by a return of these substances to normal concentration as the animal recovers. A small increase in the size of the adrenal occurs. Typical examples of this type of adrenal response are produced by an acute nonfatal hemorrhage, a short bout of muscular exercise, a single dose of very short acting drugs as epinephrine or histamine. The changes in the adrenal characterized as Type 1 can be reproduced by the injection of a single dose of ACTH.

Type 2. *A very gradual change in the internal or external environment.*

Here there is a very gradual increase in the demand for cortical hormone which results in an equally gradual increase in pituitary adrenocorticotrophic activity. The concentration of sudanophilic substance, cholesterol and ascorbic acid of the adrenals remain essentially unchanged. A gradual increase in size of the gland occurs and it is apparent that new secretory units can be constructed at a rate sufficient to meet the increasing demands. Typical examples of this type are produced by fasting, seasonal changes in temperature, and pregnancy.

Type 3. *An intense continuous stress ending in death.*

There is a very great and continuous demand for cortical hormone resulting in a maximum rate of elaboration of ACTH from the pituitary. The concentration of sudanophilic substance, cholesterol and ascorbic acid falls rapidly and remains at a very low level until the

time of death. The gland is laying down secretory units at a maximum rate, as evidenced by its marked hypertrophy. The amount of this hypertrophy is proportional to the time which elapses between the onset of the stress and death. Typical examples of this type of adrenal response are produced by lethal doses of toxins, infectious disease leading to a fatal outcome, and burn, hemorrhagic and traumatic shock.

Type 4. *Recovery from a period of severe stress or adaptation to stress.*

In this case the demand for cortical hormone is reduced following a period of stress and the pituitary returns to a low state of functional activity. During the period of stress the adrenal becomes enlarged and depleted of sudanophilic substance, cholesterol and ascorbic acid. Upon removal of the stress these metabolic constituents accumulate in a manufacturing plant which is overexpanded for the needs of the organism under optimal conditions of the environment. — The initial depletion of the cholesterol content of the gland represents the toxic phase of the response. The return to normal and subsequent increase of concentration above normal represent the recovery phase. This type of adrenal response also occurs when an animal adapts to a continuous applied noxious stimulus. It is of interest to note that the phase of accumulation of cholesterol and ascorbic acid in a hypertrophied gland correspond to the period of increased crossed resistance, which follows stress.

Type 5. *Dysfunction of the pituitary attended by hypersecretion of ACTH.*

In this case the organism has no need for increased amounts of cortical hormone but due to some dysfunction of the pituitary the adrenal cortex is stimulated to increased secretory activity. The adrenal is maximally increased in size and continuously depleted of its sudanophilic substance, cholesterol and ascorbic acid. The clinical example of this is Cushing's disease. The picture can be reproduced in the laboratory by chronic administration of large doses of ACTH.

Type 6. *Dysfunction of the pituitary attended by hyposecretion of ACTH.*

In this case the adrenal cortex atrophies as a result of pituitary

hypofunction. The sudanophilic material, the cholesterol, and the ascorbic acid of adrenal become inert at a high concentration. They are nonresponsive to changes in the internal and external environment. A clinical example of this type is found in pan-hypopituitarism (Simmonds' disease). In the laboratory it is produced by hypophysectomy.»

On the Effect of Diseases on the Adrenal Cortex

The literature contains frequent mentions of adrenal changes present in connection with different diseases, of which the main features are reviewed in the following.

In the 1910's LÖSCHKE, WELTMANN, GOLDZIEHER etc., advanced the view that death in connection with acute fever diseases, particularly toxic diseases, such as dysentery and diphtheria, was due to adrenal insufficiency. The fact that cellular degenerations, small haemorrhages, round cell infiltrates, etc., have often been found in the adrenals on obduction, has been considered as supporting this assumption (VIRCHOW 1857, OPPENHEIMER & LOEPER 1901, SCHEEL 1908, BABES 1908, THOMAS 1911, KELLNER 1933, MACLEAN 1937, RICH 1944, etc.). In addition, e.g. GOLDEN (1948), found signs of exhaustion in the adrenals of malaria patients. — SELYE (1946) advances the opinion that, with man, a stress of long duration (e.g. illness) can cause the development of Addison's disease.

According to some investigators, insufficiency of the adrenal cortex is often present in severe infantile gastroenteritis. MACLEAN, SULLIVAN & ZWEMER (1932), as well as Heni (1941), support this conception with the electrolytic changes found in the plasma of diarrhoeal patients. v. SZÁZS (1939, 1941), FORSELL (1947, 1948), and BARTA (1948), again, in support of this conception, give the clinical picture of the disease and the positive results from treatment with desoxycorticosterone acetate. On the other hand, it is true, DARROW (1946), and DARROW & al. (1949) consider the administration of desoxycorticosterone in these cases as clearly contraindicated. According to GOLDZIEHER (1946), the great hydrolability of infants is due to relative adrenal insufficiency, and this hydrolability again accounts for the rapidly developing condition of dehydration in connection with diarrhoea.

Furthermore, mention of adrenal changes in some diseases peculiar

to newborn and infants is also made in the literature. These questions will be dealt with in greater detail later.

Some data on the weights of the adrenals of adults who died of various diseases are given in the literature (MATERNA & JANUSCHKE 1927, ADAMS & BAXTER 1948, UOTILA & PEKKARINEN 1951), but no corresponding figures for infant material have been found.

Present Investigations

Effect of the Duration of Disease on Adrenal Weight.

SELYE (1946, 1950) and SAYERS & al. (1943—44) have shown that the size of the adrenals is decisively affected by the duration of the stress in question. It may be justifiable, therefore, to consider the effect of the duration of the disease on the weight of the adrenals in the present material.

It has sometimes been difficult to judge the duration of the disease, e.g. if the patient has had a chronic disease but his death has resulted from some acute infectious disease for instance. In such cases an attempt has been made to estimate the patient's principal disease on the basis of clinical records and obduction findings, and to compute the duration of the disease accordingly. Premature babies have been excluded from this material as with them, in most cases, the duration of the disease is equal to the age.

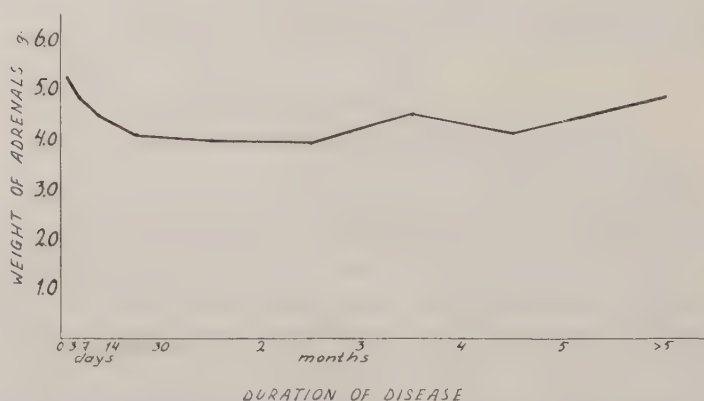
The material has been divided up into two groups; newborn, or those who died at the age of 0-14 days, and those who died at the age of 15 days to 2 years, since, as can be seen from Table 5, absolute adrenal weights at the age of 0-14 days are considerably higher than with the second group.

The adrenal weights of the newborn as a function of the duration of disease are given in Table 13.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days	6.92 ± 0.56	3.90—12.00	16
4— 7 »	6.16 ± 0.49	3.05—11.10	14
8—14 »	5.94 ± 0.41	4.40— 8.70	10

Table 13. Weight of adrenals as a function of the duration of disease with fullterm infants of 0—14 days.

Table 14 and Graph 11 show the absolute weights of the adrenals as a function of the duration of disease with children of 15 days to 2 years.



Graph 11. Development of the weight of the adrenals, according to the duration of disease: fullterm infants of 15 days to 2 years of age.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days	5.19 ± 0.32	3.08—7.90	17
4— 7 »	4.84 ± 0.32	2.07—7.00	20
8—14 »	4.44 ± 0.24	2.90—6.57	17
15—30 »	4.10 ± 0.19	2.00—6.80	36
1— 2 months ...	3.94 ± 0.24	1.63—8.25	35
2— 3 » ...	3.91 ± 0.33	1.78—7.10	19
3— 4 » ...	4.48 ± 0.50	2.50—8.15	9
4— 5 » ...	4.09 ± 0.26	3.15—5.08	8
over 5 » ...	4.77 ± 0.31	2.58—6.42	13

Table 14. Absolute weight of adrenals by the duration of disease with full-term children of 15 days to 2 years.

The weight of the adrenals seems to be at its highest in patients who have died from diseases of the shortest duration (0—3 days). With extending duration of disease the average adrenal weight first drops, and from the 15—30-day duration of disease onwards there is little variation in the weight of the adrenals. An exception is constitut-

ed by the fairly high average adrenal weight found in the last group (duration of disease over 5 months). This may be due to the fact that the group includes a considerable number of patients suffering from e.g. congenital hydrocephalus or meningocele, who died of some acute infectious disease or from post-operative shock, and who could possibly have been placed in some other duration of disease group.

Effect of the Duration of Disease on the Weight of the Adrenals in Different Diseases.

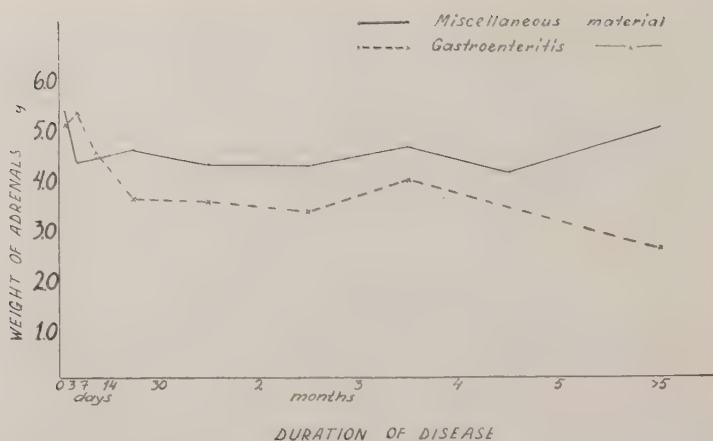
Table 2 shows that most of the disease groups are so small that the effect of the duration of disease on the weight of the adrenals cannot be demonstrated. An exception is constituted by the patients who died of gastroenteritis, totalling 72. In the following the intention is to study the development of the weight of the adrenals of patients who died of diarrhoea. The remaining material, termed »miscellaneous material», will be used as a comparison.

Table 15 and Graph 12 show the adrenal weights of diarrhoea patients as a function of the duration of disease.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0— 3 days	5.07 ± 0.40	3.60—7.12	8
4— 7 »	5.30 ± 0.34	3.80—7.00	10
8—14 »	4.49 ± 0.28	3.20—5.70	9
15—30 »	3.64 ± 0.20	2.32—5.40	18
1— 2 months ...	3.60 ± 0.36	1.63—6.50	17
2— 3 » ...	3.35 ± 0.20	2.30—3.99	7
3— 4 » ...	3.96	3.60—4.32	2
4— 5 » ...	—	— —	—
over 5 » ...	2.58	— —	1

Table 15. Weight of the adrenals as a function of the duration of disease: gastroenteritis material.

The corresponding figures for the miscellaneous material are given in Table 16 and Graph 12.



Graph 12. Development of the weight of the adrenals according to the duration of disease: miscellaneous and diarrhoea materials.

Duration of disease	Weight of adrenals, g		Number of instances
	Average	Range	
0—3 days.....	5.30 ± 0.51	3.08—7.90	9
4—7 »	4.38 ± 0.51	2.07—6.60	10
8—14 »	4.49 ± 0.40	2.90—6.57	8
15—30 »	4.55 ± 0.29	2.00—6.80	18
1—2 months ...	4.27 ± 0.32	2.90—8.25	18
2—3 » ...	4.24 ± 0.50	1.78—7.10	12
3—4 » ...	4.64 ± 0.72	2.50—8.15	7
4—5 » ...	4.09 ± 0.26	3.15—5.08	8
over 5 » ...	4.95 ± 0.28	3.45—6.43	12

Table 16. Weight of the adrenals as a function of the duration of disease: miscellaneous material.

A comparison of the above tables and graphs shows that no difference worth mentioning is observable in the adrenal weights of patients dying suddenly (duration of disease 0—3 days) in the miscellaneous and the diarrhoea materials, whereas a distinct difference obtains in cases of lengthier duration of illness. The curve of the miscellaneous material, from the 4—7-days' duration group, remains fairly even, apart from a slight rise with durations exceeding 5 months. In the gastroenteritis material again, the curve shows a distinct fall from the duration group of 8—14 days onward, and the absolute

values are much lower than in the miscellaneous material. Calculus of correlation show that the decline in weight of the adrenals in diarrhoea patients is highly significant. The difference between the curves for the miscellaneous and the gastroenteritis materials is statistically significant.

Deviation Percentage of Adrenal Weight from the So-Called Normal Weight as a Function of Duration of Disease.

The variations in the absolute weight of the adrenals in accordance with the duration of the disease have been discussed above. The results are somewhat indefinite due to the fact that, as shown by Graph 2, the weight of the adrenals varies considerably in the different age groups, and that the breakdown of infants of different ages into groups of disease duration is completely haphazard.

To clarify the matter, a calculation has been effected in each case to show how much the adrenals deviate from the so-called normal weight for the age in question; the average values of these deviations have been calculated by groups of disease duration. There being no normal material proper available, it has been necessary to employ as «normal values» the average adrenal weights shown in Table 5. Although no true picture can be obtained with certainty in this way either, it is nevertheless of interest to compare the results thus obtained with those calculated from the absolute weights.

Duration of disease	Deviation from normal value %		Number of instances
	Average	Range	
0—3 days.....	+ 7	—22 — +50	8
4—7 »	+19	— 9 — +75	10
8—14 »	+11	—20 — +54	9
15—30 »	— 9	—41 — +50	18
1—2 months ...	— 3	—48 — +50	17
2—3 »	—21	—42 — —10	7
3—4 »	— 9	—10 — — 8	2
4—5 »	—	— — —	—
over 5 »	—44	— — —	1

Table 17. Gastroenteritis material. Deviations of adrenal weights as percentages of the so-called normal weight, by groups of disease duration.

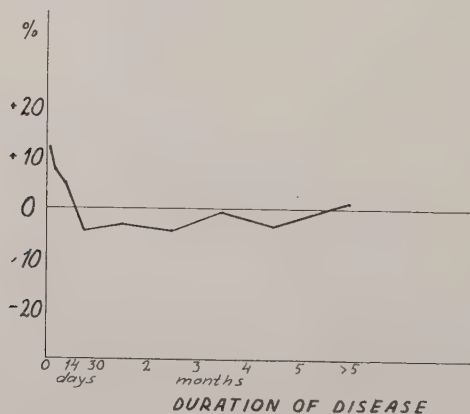
Duration of disease	Deviation from normal value %		Number of instances
	Average	Range	
0—3 days.....	+17	—23 — +97	9
4—7 »	—3	—47 — +47	10
8—14 »	±0	—28 — +42	8
15—30 »	+1	—56 — +48	18
1—2 months.....	—4	—34 — +87	18
2—3 »	+6	—50 — +80	12
3—4 »	+2	—39 — +57	7
4—5 »	—4	—20 — +27	8
over 5 »	+4	—27 — +40	12

Table 18. Miscellaneous material. Deviations of adrenal weights as percentages of the so-called normal weight, by groups of disease duration.

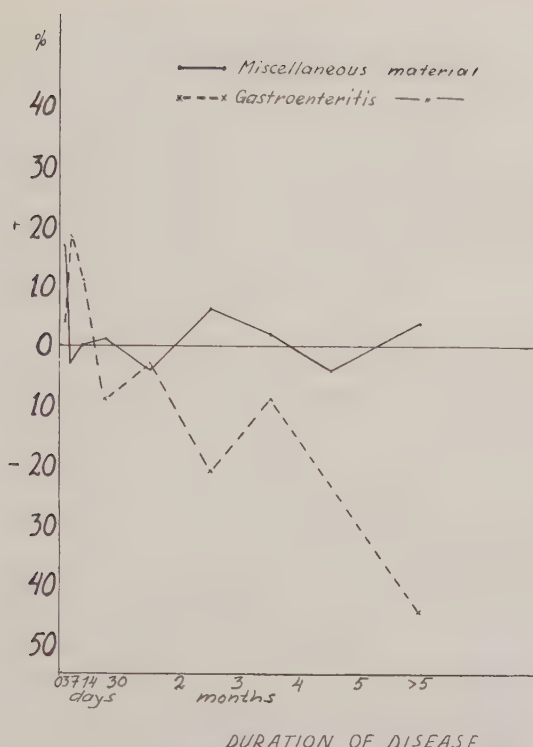
The following denominations have been used: normal value = 0, and the deviations are given as + or — percentages of this value.

Graphs 13 and 14 show the result in total. diarrhoea and miscellaneous materials.

Tables 17 and 18 give the results of the diarrhoea and miscellaneous materials specified in greater detail.



Graph 13. Adrenal weights as percentages of the so-called normal weight, grouped according to the duration of disease: fullterm infants of 15 days to 2 years of age.



Graph 14. Adrenal weights as percentages of the so-called normal weight, grouped according to the duration of disease: miscellaneous and diarrhoea materials.

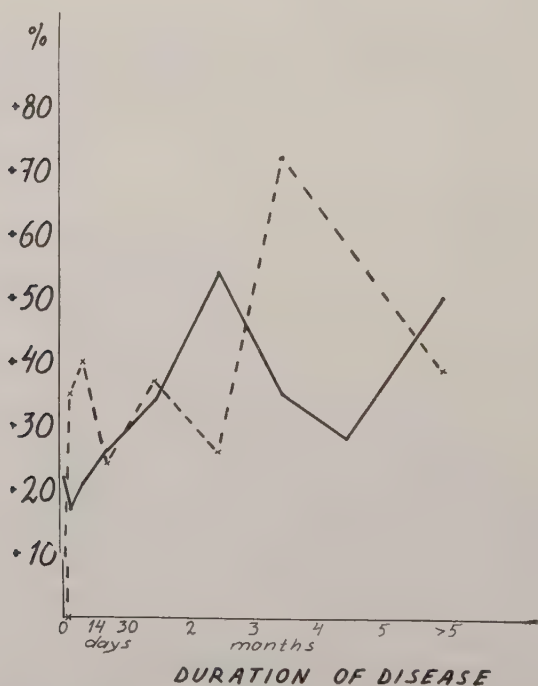
Comparison of the miscellaneous and diarrhoea materials thus obtained shows that up to a disease duration of 1–2 months no statistically demonstrable difference can be seen in the different groups. The mean value obtained for those with a disease exceeding 2 months in duration in the miscellaneous material is $+3 \pm 4.6$, and in the diarrhoea material -21 ± 4.0 . The difference between these figures and the mean error of difference is $+24 \pm 6.1$, or the difference = approx. 4 times the mean error, which result is highly significant.

When considering Graph 14, the attention is also attracted by the fact that the miscellaneous material curve from the disease duration group of 4–7 days onward displays only slight deviations from the normal value, whereas the diarrhoea curve follows a declining course for disease durations of 14 days and over. It can be demonstrated that this decline of the diarrhoea curve is statistically significant.

On the Influence of the Duration of Disease on the Relative Weight of the Adrenals.

A review of variations in the relative weight of the adrenals connected with the duration of the disease must take into consideration the great dependence of this value on the age and nutritional condition of the child. Hence, the graphs illustrating this aspect of the problem have been worked out as follows.

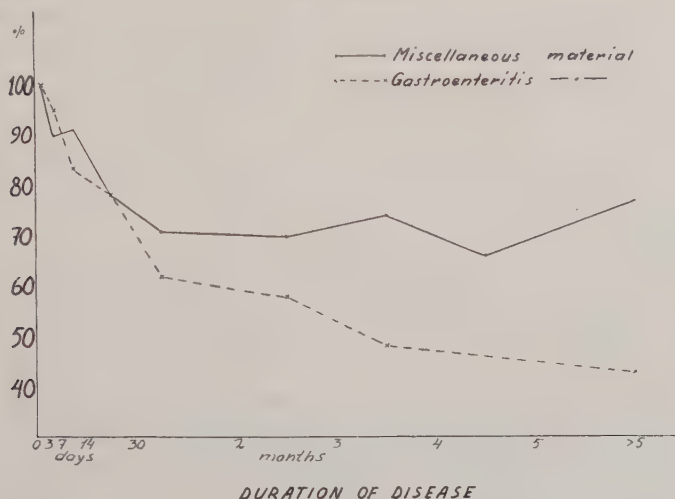
As «normal» have been considered the relative weights in the different age groups calculated from the ideal weights shown in Graph 3. In each case a calculation has been made to show how much the relative weight, computed from the weight at death, dif-



Graph 15. The relative weights of the adrenals as percentages of the so-called normal value, grouped according to the duration of disease: miscellaneous and diarrhoea materials. ————— = Miscellaneous material
 - - - - - = Gastroenteritis »

fers from the «normal value». From results obtained in this way the mean values, given as + and - percentages, have been calculated by duration of disease groups.

Graph 15 shows the development of the relative weight calculated in this way for the miscellaneous and diarrhoea material. This should be studied in conjunction with Graph 16, which shows the loss in body weight calculated as a percentage of the ideal weight, grouped according to the duration of the disease.



Graph 16. Average loss in weight — as a percentage of the so-called ideal weight — as a function of the duration of disease: miscellaneous and diarrhoea materials.

Graph 15 shows that the relative weight is somewhat increased in the group of rapid deaths. In this group the weight at death does not differ from the ideal weight to any degree worth mentioning (Graph 16), and hence this increase in relative weights is not due to the drop in body weight. For patients with a lengthier duration of disease the relative weights vary a great deal in both graphs (+30—+70. The values are throughout considerably higher than the «normal» values. With these patients the weight at death, as a rule, has been distinctly below the ideal weight (Graph 16). This result indicates that the adrenals do not diminish in the same proportion as the patient loses weight. However the relative weight of the adrenals does not increase in the same proportion as the body weight is reduced, which

is obvious, as it was seen from the absolute weights that in chronic cases, particularly with diarrhoea patients, a reduction in the size of the adrenals can be observed.

Results of Studies of the Effect of Duration of Disease on the Weight of the Adrenals.

As no comprehensive infantile material on the development of the weight of the adrenals according to the duration of disease has been found in the literature, no comparison material exists for the results quoted above. To summarise the results obtained it can be stated that:

1. *With patients who died of a disease of short duration, the absolute weight of the adrenals is distinctly higher than with those who died after a long disease.*

2. *With infants who died of diarrhoea, the absolute weight of the adrenals is continuously reduced after the initial increase, finally attaining subnormal values.*

3. *In the «miscellaneous» material, the absolute weight of the adrenals, after the initial rise, is fairly constant, in the first place perhaps «normal», from the 4—7-day disease duration group onwards.*

4. *The weights of the adrenals have been calculated as percentages of the «normal weights» of infants of the same age, and the results grouped according to the duration of disease. The results obtained in this way are similar to those calculated above from the absolute weights.*

5. *The relative weights of the adrenals have been dealt with according to the principle mentioned in item 4 above. The values obtained in this way are higher than normal throughout the material. However, the rise in relative weight suggested by the loss of body weight was not observed. This fact was evident with the diarrhoea patients particularly, for in cases of prolonged illness especially the weights of these patients have decreased a great deal.*

VII. ON THE LIPOIDS OF THE ADRENAL CORTEX.

PLECKNICK (1902) has found lipoids as early as in the cortex of a 5 cm long foetus. At the moment of birth, according to KEENE & HEWER and STARKEL & WEGRZYNOWSKI, lipoids are present in the peripheral parts of the cortex only, whereas KAWAMURA (1911) has shown that sudanophilic lipoids are present in the peripheral parts only and birefringent lipoids throughout the cortex.

After the foetal period it is practically impossible to obtain any normal material on adrenal cortex lipoids for, according to SELYE (1946), diseases, traumata, etc., very readily affect the lipid content of the adrenals.

ZWEMER (1936), BOURNE (1949), GOLDZIEHER (1946), etc., have given the following description of the lipoids of the adrenals in assumedly normal conditions of rest:

Zona glomerulosa: fair amount of small-granule fat formation.

Exterior part of fasciculata: plenty of large lipid granules.

Interior » » » : less lipoids, and the granules are smaller.

Zona reticularis: a fair amount of small-granule lipoids.

According to the above investigators, the distribution of sudanophilic lipoids and birefringent substances are roughly equal.

Lipoid Content of Adrenal Cortex in Different Diseases

The lipid content of the adrenal cortex in the various diseases has been studied a great deal, and the results are fairly varying. By way of general summary it can be said that, as a rule, adults who have died of acute diseases display fairly little, and those who have died of chronic diseases a fairly large amount of lipoids (LÖSCHKE 1910, KAWAMURA 1911, LANDAU 1913, GRAHAM 1916, PFEIFFER 1919, DEUCHER 1923, MATERNA & JANUSCHKE 1927, THADDEA 1938, LIEBEGOTT 1944, GOLDZIEHER 1946, VERZÁR 1948, ADAMS & BAXTER 1948, ROGERS & WILLIAMS 1949). WELTMANN (1913) has shown that

the hyperacutely dead generally have plenty of lipoids. According to him, the lipid content varies considerably less with children than with adults. BORBERG (1915) states that the adrenals of children generally contain less lipoids than those of adults. The variations in the lipid content of the adrenal cortex of infants suffering from different diseases have been studied e.g by TOBECK (1928), BLUMENSAAT (1929), ROSENBAUM (1931), and MENTEN & SMITH (1936). Each of them comes to the conclusion that, generally speaking, the adrenals of infants are relatively rich in lipoids, and that the most distinct loss of lipoids can be demonstrated in those who have died of chronic infectious diseases. All the materials, however, reveal very great individual variations. The lipid content in the different zones of the adrenal cortex, according to the above-mentioned researchers, varies greatly with different diseases, but no distinct conformity to rule can be shown. MENTEN & SMITH have found that the stillborn and those who died at the age of a couple of days are very short of both sudanophilic and birefringent substances. Unfortunately, these researchers paid no detailed attention in their investigations to the effect of the duration of disease on the lipid content, nor have they recorded the weights of the adrenals.

With infants who died of gastro-enteric intoxication KAWAMURA was unable to find any evidence of double refractive substances. The same result has been attained by BORBERG. WELTMANN again has found a fairly large amount of lipoids in the adrenals of diarrhoea patients who have suffered from a disease of lengthy duration.

HUEBSCHMANN (1921) and STEPHANI (1923) studied the lipid content of the adrenals of infants who died of gastroenteritis. According to them, acute cases generally display low amounts of sudanophilic lipoids and birefringent substances; particularly marked is their absence from the zona glomerulosa. In chronic cases the results are varying. With three atrophic infants STEPHANI found adrenals rich in lipoids. — As control material he employed infants who had died of pneumonia, who generally had a fairly large amount of lipoids.

HALLMAN & AHVENAINEN (1950) have found great variations in the lipid content of the adrenals in 47 infants who died of gastroenteritis. They have been unable to demonstrate any loss of lipoids from the zona glomerulosa.

Gastro-enteric patients usually display disturbances in mineral

metabolism, e.g. in the Na and K content of the organism (GAMBLE 1947, DARROW 1946, HALLMAN,). NICHOLS & HILL (1948) found in animal tests that, in the absence of Na and K, lipoids disappear from the exterior parts of the adrenals. DEANE, SHAW & GREEP (1948), similarly, have shown signs of increased activity in test animals in the zona glomerulosa (e.g. loss of lipoids) when there is a shortage of Na or of both Na and K. If the organism contains an excess of Na, lipoids accumulate in the area of the zona glomerulosa. With infants who had died of gastroenteritis, HALLMAN & TÄHKÄ (1950) were unable to establish any correlation between the Na and K content of serum and erythrocytes and the lipoid content of the zona glomerulosa.

On Qualitative and Quantitative Determinations of Adrenal Lipoids

The lipid content of the adrenals has been widely investigated both chemically and histologically, and the results attained by the different investigators are even very contradictory.

FEX (1920) and HERMANN (1940) emphasise the inaccuracy of histological methods of determination compared with the chemical, whereas KAY & WHITEHEAD (1935), KNOUFF & al. (1941), SAYERS & al. (1943—44), and ROGERS & WILLIAMS (1947) show that the results attained with these two methods are fairly well correlated.

The results of some investigators may be mentioned as examples of chemical lipid determinations:

NEYMANN (1939) effected chemical determinations of the cholesterol content with foetuses of 6—9 months and gives the following average values:

free cholesterol	224	mg%	of the	wet	weight	of	adrenals
ester	»	298	»	»	»	»	»
total	»	522	»	»	»	»	»

With fullterm newborn the cholesterol content, according to BEUMER (1921), is 1340 mg%, and according to CHAUFFORD & al. (1914) 3600 mg% of the dry weight of the adrenals.

HERMANN and BEUMER have carried out chemical cholesterol determinations with infants and LAGE (1940) with children of 2—6 years of age. The total cholesterol content varies between 1000 and 5500 mg% of the dry weight of the adrenals. No regularity can be

observed in the proportion of free cholesterol and cholesterol ester. The lowest values were found with patients who had died of gastro-enteric intoxication.

Present Investigations

Comparison of Chemical and Staining Results.

Table 19 specifies the cases in which both chemical and histological lipid investigation was carried out.

Case No	Age	Duration of disease	Diagnosis	Chemical ¹⁾ determinations			Histological ²⁾ determinations		
				Total lipids	Total chol.	Est. chol.	S—R	L—B—S	Pol
79/49	1 day	1 day	Praematurus	9.31	1.90				
92/49	2 days	2 days	"	23.87	1.75			+	
91/49	3 "	3 "	"	31.59	9.08			++	
93/49	3 "	3 "	"	28.29	3.67			++	
78/49	25 "	25 "	"	11.66	7.25			++	
172/49	22 "	10 "	Gastro-enteritis	51.53	9.91	7.12	++	+++	++
231/49	2 months	13 "	"	47.44	3.72	1.55	++	++	++
227/49	2 1/2 "	19 "	"	32.55	3.82	2.34	++	++	++
261/49	3 "	30 "	"	61.72	10.53	7.88	++	+++	++
171/49	3 1/2 "	20 "	"	45.00	4.59	2.68	++	++	++
259/49	3 1/2 "	18 "	"	32.61	4.28	2.65	++	++	++
222/49	5 "	21 "	"	52.74	2.63	1.86	++	++	++
42/49	5 1/2 "	2 "	"	71.28	0.93	0.30	++	0	+
184/49	6 "	21 "	"	81.98	16.05	13.51	++	+++	+++
48/49	9 "	1 "	"	33.27	1.18	0.84	++	0	
247/49	10 "	3 "	"	34.95	4.24	2.93	++	++	++
83/49	15 days	5 "	Pneumonia	31.20	3.84	2.07	++	+++	
43/49	2 months	1 1/2 months	Stenosis pylori	26.50	3.70	3.08	++	++	
63/49	9 1/2 "	5 days	Status post laparotomy	52.36	1.24	1.06	++	0	

¹⁾ Results as percentages of the dry weight of adrenals

²⁾ S—R = Scarlet-red staining

L—B—S = Liebermann—Burchard—Schultze staining

Pol = result with polarized light.

Table 19. Chemical and histological determination of lipoids.

The results show that the lipid content varies considerably in the different cases. In addition, it is noted that the total lipid and cholesterol contents do not always follow the same course, as is seen e.g. from Cases 42/49 and 78/49.

The extent to which the lipid contents estimated from the chemical and histological preparations in the present material are correlated in the material, is seen from Table 20.

Lipoid content		Number of cases
Histological determination	Mean value of chemical determinations	
Scarlet-red staining	Total lipid content %	
0	—	0
+	27.1	8
++	46.3	9
+++	—	0
++++	71.3	2
Liebermann—Burchard—Schultze staining	Total cholesterol content %	
0	1.12	3
+	2.91	6
++	4.20	4
+++	7.89	4
++++	13.56	2
Double refracting substances	Total cholesterol content %	
0	—	0
+	3.81	5
++	7.07	2
+++	10.53	1
++++	16.05	1

Table 20. Relationship of chemical and histological lipid determinations.

According to Table 19, the results obtained by chemical and histological methods of determination do not correspond in all individual cases. However, as can be seen from Table 20, the mean value results with the different staining methods are fairly similar. Unfortunately, the material is so small that the matter cannot be proved mathematically.

Lipoid Content in Different Disease Groups.

Fig. 1 shows the percentage distribution of the lipid content ascertained by the different staining methods in the miscellaneous and diarrhoea materials, and with premature infants and fullterm newborn of 0—14 days of age.

LIPOID CONTENT



I = MISCELLANEOUS MATERIAL

II = GASTROENTERITIS — " —

III = PREMATURE INFANTS

IV = NEWBORN, FULL-TERM INFANTS

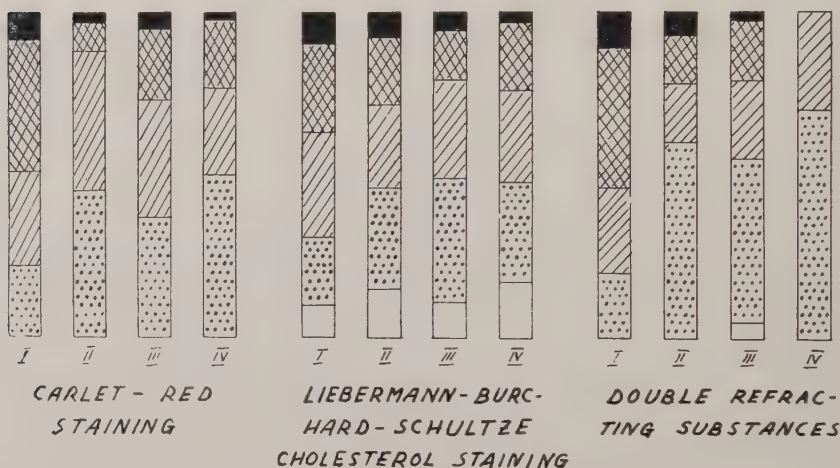


Fig. 1. Lipoid content in the different disease groups and by the different staining methods.

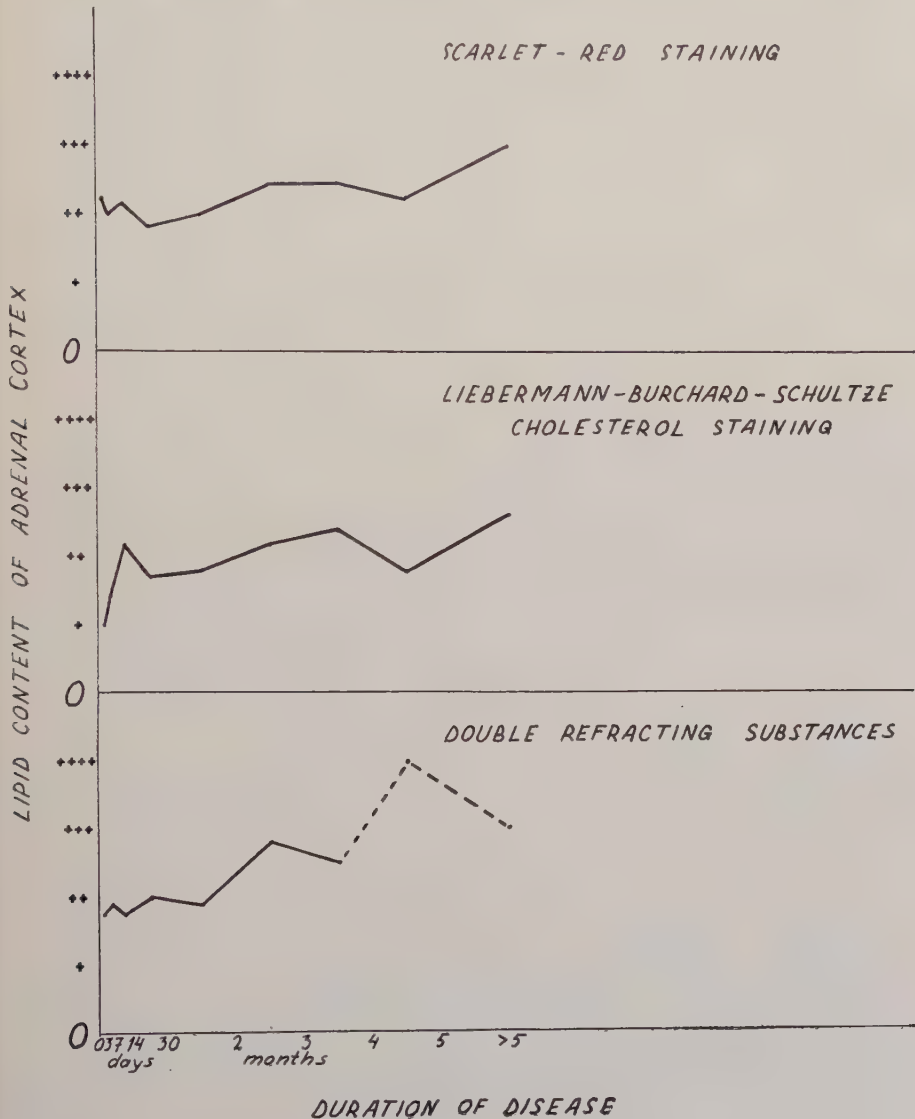
The columns show that the only difference fairly distinctly discernible in all the different staining methods is that the lipid content in the miscellaneous material cases, on the average, is somewhat higher than in the other groups.

Influence of Duration of Disease on Lipoid Content.

In order to make the material conform in this respect to the weight materials above, principal attention has been paid to fullterm infants

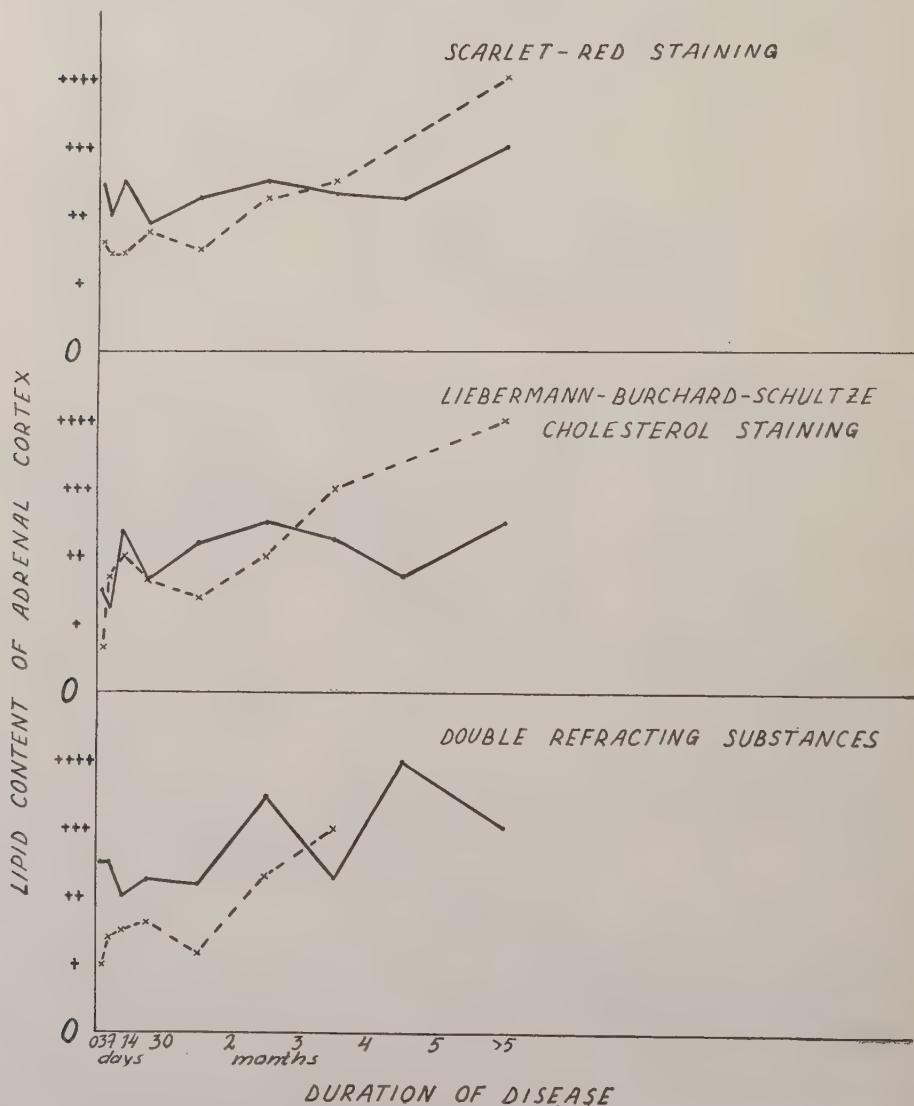
of 15 days to 2 years. The variations in the lipoid content of the total material and of the miscellaneous and diarrhoea cases have been dealt with separately.

Average lipoid content, as a function of the duration of disease, in the total material, is shown by Graph 17.



Graph 17. Lipoid content as a function of the duration of disease: fullterm infants of 15 days to 2 years of age.

The same is shown for miscellaneous material and diarrhoea material in Graph 18.



Graph 18. Lipoid content as a function of the duration of disease: miscellaneous and diarrhoea materials.

The graphs show that the tendency in all materials seems to be that those dying from acute diseases, on an average, have less lipoids than those who died of a disease of lengthy duration. Calculus of correlation show that the rise of the cholesterol staining curve in the diarrhoea material is significant. In the miscellaneous material, again, the rise of the curve cannot be proved to be statistically reliable. The dissimilarity between the curves of the diarrhoea and miscellaneous materials is statistically almost significant.

With newborn (0—14 days) no distinct differences due to the duration of the disease can be shown in the lipid content.

*Lipoid Content in the Different Layers of the Cortex.
Premature and Newborn Infants.*

Table 21 shows the variations in the lipid content of the different layers of the adrenal cortex of premature infants. In these cases it is often impossible to divide the permanent cortex into different zones with any certainty, for which reason the terms »exterior and interior part of the permanent cortex» will be used. The table has been computed from cholesterol staining results.

Table 22 shows the same for fullterm newborn.

On the basis of Table 21 it can be said that the lipid content is somewhat lower with premature infants in the young age groups than in the older groups. As with premature infants generally age = duration of disease, this phenomenon is fully compatible with the observation that the adrenals of persons who have died of chronic diseases are as a rule rich in lipoids.

Both tables (21 and 22) reveal that complete loss of lipoids is somewhat more frequent in the area of the permanent cortex than that of the foetal cortex. However, individual variations are so considerable and the materials in the different age groups of such varying extent that no distinct law-like regularity can be established on the basis of the present material.

Miscellaneous and Diarrhoea Material.

As Graphs 17 and 18 show, the lipid content of the adrenals varies considerably according to the duration of the disease. Hence, the lipid contents in the different cortical layers of patients in the miscellaneous and gastroenteritis material are given divided up into groups according to the duration of disease. Table 23 shows these results in the miscellaneous material and Table 24 gives the same data on the gastroenteritis material.

A study of tables 23 and 24 shows that no distinct regularity is ascertainable in the variation in lipid content of the different layers of the adrenal cortex. The results do not corroborate Stephani's finding, that loss of lipoids in the zona glomerulosa is strikingly frequent with diarrhoea patients.

Results of the present Investigations into Lipoids.

The records found in the literature regarding the variations in the lipid content of the adrenals in patients who have died of different diseases, are often very contradictory. This may be due, in the first place, to dissimilarity of materials and possibly also to some extent to the different methods of determining the lipid content. Taking this into consideration, there is little point in comparing the results obtained in the present investigation with the results published by other investigators.

To summarise the results obtained it can be stated that:

1. *Lipoid determinations by chemical and histological methods are fairly well correlated. The results with the three histological methods of determination employed are fairly similar, though there are exceptions in individual cases.*

2. *The average lipid content given by all methods is greater in the miscellaneous material than in the diarrhoea, premature or newborn infant materials.*

3. *In the total material the lipid content in cases of acute disease is smaller than in those with a disease of long duration. This is only*

Age	Permanent cortex										Foetal cortex										Total number of cases	
	Exterior part					Interior part																
	0	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+		+
0—7 days	15	20	7	—	1	19	13	9	1	1	10	15	16	2	—	—	—	—	—	—	—	43
8—14 »	4	5	2	1	—	3	3	5	1	—	2	2	2	6	—	—	—	—	—	—	—	12
15—30 »	2	2	1	—	1	1	3	1	—	1	1	2	0	3	—	—	—	—	—	—	—	6
1—2 months	2	3	3	1	1	2	1	2	4	1	1	1	3	3	2	—	—	—	—	—	—	10
2—3 »	—	3	1	2	1	—	2	2	2	1	1	—	2	3	1	—	—	—	—	—	—	7
3—4 »	—	—	1	4	—	—	—	2	3	—	—	1	1	3	—	—	—	—	—	—	—	5
4—5 »	—	—	—	1	—	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—	1
5—6 »	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6—9 »	—	—	—	—	1	—	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	1
Total	23	33	15	9	5	25	22	21	12	5	15	21	24	21	4	—	—	—	—	—	—	85

Table 21. Cholesterol content of the different zones of the adrenal cortex in premature infants.

Age	Permanent cortex										Foetal cortex										Total number of cases
	Exterior part					Interior part															
	0	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	
0-7 days	12	3	7	2	1	8	7	7	3	—	3	8	6	7	1						25
8-14 »	3	1	2	1	1	2	2	1	2	1	3	1	1	2	1						8
Total	15	4	9	3	2	10	9	8	5	1	6	9	7	9	2						33

Table 22. Cholesterol content of the different zones of the adrenal cortex in newborn, fullterm infants.

Duration of disease	Zona glomerulosa					Zona fasciculata					Zona reticularis or foetal cortex					Total number of cases
	0	+	+	+	+	+	+	+	+	+	0	+	+	+	+	
0—3 days	2	2	1	1	—	—	—	—	—	—	3	—	2	1	—	6
4—7 »	3	—	4	2	—	—	—	—	—	—	4	—	4	1	—	9
8—15 »	1	1	2	3	1	1	2	3	2	—	1	2	2	3	—	8
15—30 »	1	7	4	1	—	—	1	4	5	3	1	3	5	4	—	13
1—2 months	1	5	3	5	1	1	4	—	6	4	3	1	4	6	1	15
2—3 »	2	2	—	3	2	2	1	2	2	2	—	4	1	2	2	9
3—4 »	—	1	1	4	1	—	1	1	3	3	1	—	2	4	—	7
4—5 »	2	—	3	1	—	—	2	1	2	1	2	—	2	2	—	6
over 5 »	1	—	2	2	4	2	—	—	1	2	2	—	2	2	3	9
Total	13	18	20	22	9	17	12	26	20	7	17	10	24	25	6	82

Table 23. Miscellaneous material. Cholesterol content of the different cortical zones, grouped by the duration of disease.

Duration of disease	Zona glomerulosa					Zona fasciculata					Zona reticularis or foetal cortex					Total number of cases
	0	+	++	+++	++++	0	+	++	+++	++++	0	+	++	+++	++++	
0—3 days	2	2	1	—	—	4	1	—	—	—	3	2	—	—	—	5
4—7 »	2	3	—	2	—	4	2	—	1	—	1	2	2	2	—	7
8—14 »	—	1	—	2	—	1	—	—	2	—	—	1	1	1	—	3
15—30 »	—	9	1	4	1	8	2	2	2	1	4	6	2	2	1	15
1—2 months	2	5	2	3	—	5	—	4	3	—	5	—	4	3	—	12
2—3 »	—	1	4	—	2	1	2	2	1	1	2	2	1	1	1	7
3—4 »	—	—	—	1	1	—	1	—	—	1	—	—	1	—	1	2
4—5 »	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
over 5 »	—	—	—	—	1	—	—	—	—	1	—	—	—	—	1	1
Total	6	21	8	12	5	23	8	8	9	4	15	13	11	9	4	52

Table 24 Gastroenteritis material. Cholesterol content of the different cortical zones, grouped by duration of disease.

mathematically demonstrable, however, by cholesterol staining, with those who died of diarrhoea.

4. No distinct law-like regularity in the lipoid content of the adrenocortical zones is present in the different disease or duration of disease groups.

VIII. THE ADRENALS IN SOME PARTICULAR DISEASES

In the foregoing, only premature infants and diarrhoea patients have been dealt with as separate groups, being numerous enough to allow of mathematical corroboration.

However, there are several diseases peculiar to newborn and to infants in which adrenal changes have often been found. Although these groups are not particularly large in the present material, it may be justifiable to study these cases in slightly greater detail.

Cerebral Deformities

Towards the end of the 19th century, LOMER (1884), and ZANDER (1890), found that patients with anencephalus, congenital hydrocephalus, encephalocele and other cerebral deformities often have unusually small adrenals. The same was observed, particularly with anencephaluses by ELLIOTT & ARMOUR, GOLDZIEHER, EKHOLM & NIE-MINEVA. LANDAU explains the small adrenals as being due to the fact that the involution of the foetal cortex is already fairly complete in the foetal period. McNEILL reports 5 anencephaluses; with one of them only had the involution of the foetal cortex advanced unusually far.

Present Cases.

Table 25 shows the cerebral deformities included in the present material.

The present material includes only one anencephalus, Case No 183/49. The patient also had other deformities, e.g. large cystic

Case No	Age	Diagnosis	Weight of adrenals, g	Average adrenal weight at same age	Foetal cortex %	Average foet. c. % at same age
183/49	20 min.	Anencephalus ...	7.00	6.50 ± 0.37	84	77
56/49	5 days	Meningoencephalocele occipit.	5.83	6.50 ± 0.37	69	65
94/49	2 months	Encephalocele reg. frontalis	2.54	3.51 ± 0.22	42	19
268/48	5½ »	Hydrocephalus	3.80	4.46 ± 0.27	11	8
73/49	5½ »	»	4.37	4.46 ± 0.27	—	8
79/49	6 »	» cong.	4.97	4.69 ± 0.24	—	5
190/49	6 »	»	3.43	4.69 ± 0.24	—	5
147/49	8 »	» cong.	3.35	4.69 ± 0.24	15	5
269/49	9 »	»	6.00	4.67 ± 0.39	—	—
39/49	9 »	» cong.	5.35	4.67 ± 0.39	—	—

Table 25. Cases of cerebral deformity.

kidneys. A fairly extensive haemorrhage could be seen in the adrenals. The involution of the foetal cortex had not advanced any further than usual.

Nor do the size of the adrenals or the involution of the foetal cortex of the other cases differ distinctly from the normal. According to Lomer, a deformity in the anterior part of the brain causes adrenal changes particularly often. Case No. 94/49 belongs to this group. This patient, it is true, had smallish adrenals, but the involution of the foetal cortex was even unusually slow. Hydrocephalus patients, again, were so old at the time of death that their foetal cortex would have practically disappeared in the normal course of events, and hence no conclusions can be drawn from this material.

Congenital Heart Disease

According to GOLDZIEHER (1946), oxygen deficiency causes an enlargement of the adrenals and retards the involution of the foetal cortex. He has found this with several patients who died of congenital heart disease, particularly with cyanotic patients, so-called blue babies.

Present Cases.

The present material includes 15 cases of death from congenital heart disease, and these cases are specified in Table 26.

Case No	Age	Cyanosis	Weight of adrenals, g	Average weight of adrenals at same age	Foetal cortex %	Average foetal cortex % at same age
51/49	1 day	+	4.99	6.50 ± 0.37	69	77
58/49	5 days	+	6.51	6.50 ± 0.37	70	68
130/49	5 »	+	7.15	6.50 ± 0.37	60	60
61/49	9 »	++	4.88	6.11 ± 0.45	46	57
217/48	10 »	++	4.40	6.11 ± 0.45	40	55
66/49	13 »	+++	5.45	6.11 ± 0.45	35	46
45/49	18 »	+	4.25	4.52 ± 0.31	41	38
146/49	1 month	++	3.52	4.30 ± 0.36	13	27
159/49	1 $\frac{1}{2}$ months	+	3.99	4.30 ± 0.36	50	27
113/49	2 $\frac{1}{2}$ »	—	4.97	3.51 ± 0.22	12	24
177/49	3 »	++	4.17	4.10 ± 0.28	13	10
224/49	3 »	—	3.52	4.10 ± 0.28	37	10
399/49	4 »	—	3.32	4.03 ± 0.30	30	7
139/49	7 $\frac{1}{2}$ »	—	4.58	4.69 ± 0.24	—	4
133/49	10 $\frac{1}{2}$ »	—	3.81	4.67 ± 0.39	—	—

Table 26. Patients who died of congenital heart disease.

From a study of Table 26 it is seen that the weight of the adrenals of these patients does not differ much from the average weight for the same age.

The involution of the foetal cortex was distinctly retarded with three patients (159/49, 224/49 and 399/49). On the other hand it was found in Cases 217/48, 66/49, 146/49 and 113/49 that the involution of the foetal cortex had advanced considerably more than is normal for the same age.

There is no relationship between cyanosis and the large size of the adrenals and retarded involution of the foetal cortex. With particularly cyanotic patients, such as 61/49, 217/48, 66/49, 146/49 and 177/49, the adrenals are relatively small, and the foetal cortex percentage is in all cases under average.

Pyloric Stenosis

In 1919 PIRIE & al. found the adrenals considerably above normal with some patients who had died of congenital pyloric stenosis. DIJKHUIZEN & BEHR. JAUDON (1948), and FANCONI & LANDOLT (1949) later published some similar cases. In spite of being a clinically distinct disease pyloric stenosis could not be demonstrated on obduction in all the cases (FANCONI & LANDOLT, DIJKHUIZEN & BEHR). Histologically an unusually large foetal cortex is sometimes found in the adrenals of these patients. This is closely connected with the so-called adrenogenital syndrome, and differential diagnosis may be difficult particularly with male infants in whom macrogenitosomia has no time to develop if the patients die young of an insufficiency of the other adrenal layers. This insufficiency, again, produces symptoms reminiscent of pyloric stenosis, such as vomiting and dehydration (DIJKHUIZEN & BEHR, JAUDON, BLACKMAN, ALLIBONE & al. 1947, DARROW 1944, CARLGREN, etc.).

Present Cases.

The present material includes 9 patients with clinically and patho-anatomically distinct pyloric stenosis.

Table 27 gives a specification of the cases.

Case No	Age	Duration of disease	Weight of adrenals, g	Average weight of adrenals at the same age	Foetal cortex %	Average foetal cortex % at the same age
247/48	1½ months	1 month	2.90	4.30 ± 0.36	24	26
350/48	»	»	4.20	4.30 ± 0.36	30	26
96/49	»	21 days	4.17	4.30 ± 0.36	30	26
169/49	»	1½ months	4.52	4.30 ± 0.36	34	26
270/48	2	»	3.00	3.51 ± 0.22	24	19
274/48	»	»	2.40	3.51 ± 0.22	26	19
369/48	»	21 days	4.30	3.51 ± 0.22	34	19
43/49	»	1½ months	2.85	3.51 ± 0.22	30	19
362/48	5	4½ »	4.40	4.64 ± 0.27	20	9

Table 27. Patients with pyloric stenosis.

Table 27 shows that no particularly large adrenals are present in the material. Deviations from the average weight are fairly small, and they are roughly equally frequent in both directions. The foetal cortex percentage, apart from Case 247/48, is somewhat above average. With three patients (369/48, 43/49 and 362/48) this difference distinctly exceeds the normal range of variation. The weights of these adrenals, however, are »normal», and hence these cases cannot be considered, at least not definitely, as representative of the above pathological picture.

On Adrenal Haemorrhages

In 1901 HAMMILL frequently found adrenal haemorrhages in stillbirths. In 1932 GOLDZIEHER & GORDON reported 84 cases of adrenal haemorrhage, 37 of them newborn. With the newborn, extensive haemorrhage produces a typical picture in which respiratory difficulties are the dominant symptom, the so-called pseudopneumonia of the newborn (GOLDZIEHER & GORDON 1930).

Extensive adrenal haemorrhages in connection with septic conditions were first reported by LITTLE (1901). The diagnosis is better known, however, as the WATERHOUSE-FRIEDRICHSEN syndrome. BAMATTER showed in 1934 that the phenomenon is especially peculiar to purulent meningitis caused by meningococcus.

GOLDZIEHER (1946) divides the haemorrhages present in the adrenals into four groups, as follows:

1. *Small haemorrhages*, present in the stroma and lymphatic spaces without tissue destruction.
2. *Diffuse haemorrhagic infarction* without tissue destruction.
3. *Destructive haemorrhages* usually begin from the zona reticularis and gradually transform the adrenal into a haemorrhagic cyst, on the surface of which some cortical tissue is found.
4. *Massive haemorrhage*: the adrenal is transformed into a sac larger than the original organ. The sac is easily ruptured resulting in retroperitoneal haematoma which may rupture into the peritoneum and result in the formation of haemoperitoneum.

Present Cases.

Small haemorrhages without tissue destruction, belonging to Group 1 above, are encountered fairly often, particularly in the area of the foetal cortex. Their significance as a factor disturbing the activity of the adrenals seems unclear on the basis of the present cases, for they were found so often and in cases with the most varied pathological picture.

Types 2 and 4 do not occur in the present material at all. Cases belonging to type 3 are three in number (240/48, 255/48 and 183/49). The significance of adrenal haemorrhage as the cause of death of these patients, however, is not clear. Case 240/48, it is true, died at the age of 6 days with symptoms fairly typical clinically, but on obduction it was found that the patient had »Kernicterus» and extensive pneumonia; hence there were several causes to account for the respiratory difficulties and other symptoms. Case 255/48 died at 3 days of age of *Pseudomonas aeruginosa* septicaemia, and Case 183/49 was an anencephalus that died immediately on birth.

The present material includes 2 patients who died of purulent meningitis caused by meningococcus, but they had no adrenal haemorrhages. Nor have extensive haemorrhages been found in connection with other septic conditions, apart from Case 255/48 mentioned above.

Patients who died of *Pseudomonas Aeruginosa* Septicaemia.

The present material contains 10 patients who died of septicaemia produced by *pseudomonas aeruginosa*. Eight of them display a very uniform course of disease, and at death they were roughly of the same age (RANTASALO 1950). It could therefore be assumed that the adrenal findings in these patients were fairly similar. Table 28 gives a specification of the cases.

The first 8 cases of Table 28 evidence the fact that individual differences are so great that no distinct adrenal changes due to the disease can be indicated.

Case No	Age	Duration of disease	Weight of adrenals, g	Average weight of adrenals at the same age	Lipoid content		
					S—R	L—B—S	pol.
255/48	3 days	1 day	7.00	6.50 ± 0.37	+		
142/49	4 »	2 days	5.16	6.50 ± 0.37	+++	+++	++
105/49	5 »	1 day	4.98	6.50 ± 0.37	+	+	+
138/49	5 »	»	12.00	6.50 ± 0.37	++	++	+
114/49	6 »	»	10.75	6.50 ± 0.37	+	+	+
174/49	6 »	»	3.90	6.50 ± 0.37	+	++	+
132/49	7 »	»	5.57	6.50 ± 0.37	+	+	+
100/49	11 »	»	5.62	6.11 ± 0.45	+	++++	++
178/49	22 »	20 days	3.95	4.52 ± 0.31	+++	+++	+++
161/49	1½ months	30 »	4.81	4.30 ± 0.36	++++	++++	++++

Table 28. Patients who died of *pseudomonas aeruginosa* septicaemia.

Miscellaneous Cases

LEWIS & PAPPENHEIMER reported two patients who died of *congenital syphilis*, whose involution of the foetal cortex was retarded. McNEILL's material contained 4 such cases but this phenomenon was not present.

The present material contains only one infant who died of *congenital syphilis* (Case 409/48). The patient was 4 months old at death, the adrenals weighed 4.08 g (average 4.03 g), and the foetal cortex percentage was 25 (average 7); hence the amount of foetal cortex was distinctly above normal.

SARASON found in 1943 that the adrenals of the newborn who had died of *erythroblastosis foetalis* were remarkably large (weight 12—17 g). A couple of similar cases were reported by ALLIBONE & al. (1947). The present material contains 3 of these patients, and their adrenal weights were 6.50, 5.10 and 8.70 g (the average adrenal weights for that age are 6.50 and 6.11 g). One of these three, therefore, had somewhat larger adrenals than the usual, but the deviations from the normal are not as great as those reported by the investigators mentioned.

Chronic adrenal insufficiency, so-called *Addison's disease*, is rare

with children in its typical form. ATKINSON in 1938 reported 40 cases with children, among which two only were under 1 year. In 1946 JAUDON collected from the literature 100 cases of infantile Addison's disease; three of them were under two years. In 1948 SIKL described a clinically typical case of Addison's disease in a child of 33 days, in which a distinct adrenal hypoplasia was found on autopsy. — The present material included no single case of Addison's disease, at least not in its typical form, either clinically or histologically.

Results

The above shows that the adrenal changes considered »typical» of certain disease groups are by no means a constant phenomenon. In most of the groups, it is true, the material available is so limited that no positive conclusions can be drawn. However, the finding, for example, that in the material of 15 cases of patients who died of congenital heart malformation there was no single instance of large adrenals with the large foetal cortex reported by GOLDZIEHER (1946), supports the opinion that this phenomenon is in no way inevitable with these patients.

To summarise the adrenal findings reported above in certain special groups of diseases it can be said that:

1. *No particularly small adrenals were found in connection with cerebral deformities (10 cases), nor did the development of their foetal cortex differ from the normal.*

2. *The size of the adrenals and the foetal cortex of infants who died of congenital heart disease (15 cases) differed to no degree worth mentioning from the average values of the total material. Severe cyanosis seemed to have no influence.*

3. *No large adrenals, with a large foetal cortex, were found in the pyloric stenosis patients of the present material (9 cases).*

4. *Fairly extensive haemorrhage in the adrenal cortex was found with three patients, but with none of them was it the only cause of death. The Waterhouse-Friedrichsen Syndrome was not demonstrated once.*

5. *In the clinically homogenous material of the patients who died of pseudomonas aeruginosa septicaemia (10 cases) great variations were*

found in the size and lipoid content of the adrenals of the different individuals.

6. The involution of the foetal cortex was retarded in the single patient of the present material who died of congenital syphilis.

7. It was found that the adrenals of the three patients in the material who died of erythroblastosis foetalis were not distinctly larger than the average.

IX. RELATIONSHIP OF THE ADRENALS TO THE THYMUS

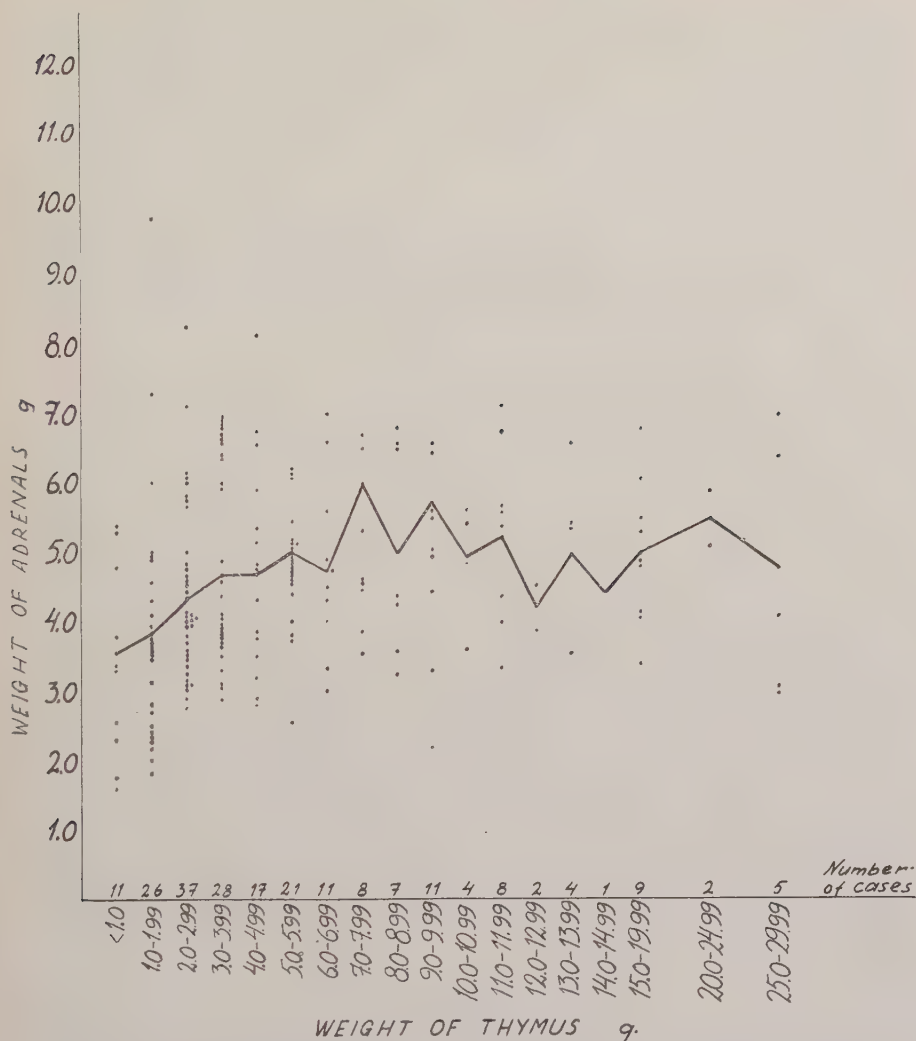
SCHRIDDE (1911) and MATTI (1912) found that hyperplasia of the thymus is often encountered in Addison's disease, and the same observation was also made e.g. by GROLLMAN (1947), VERZÁR (1948), BOYD (1943), GOLDZIEHER (1946), and SELYE (1948). JAFFE (1924), and MARINE et al. (1924), have shown by animal tests that the thymus is enlarged after adrenalectomy.

According to SELYE, the following most important changes of the thymus take place in test animals in the course of the GAS: alarm reaction causes its rapid decrease with the reduction of lymphatic tissue; in the course of the stage of resistance the thymus tends to return to its former size, diminishing rapidly again in the stage of exhaustion.

KEILMANN (1923) studied the relationship of thymus and adrenals in clinical autopsy material, and obtained no distinct correlation. SPOLVERINI (1916) attained the same result. In so-called «thymus death» BOYD has often found adrenal hypoplasia. On the other hand, CH'INK & HSUCH (1941), in a material of still-births and patients who died at birth, found hyperplasia of the thymus and adrenals usually present in one and the same individual.

Present Investigations

The interrelationship between the thymus and the adrenals in the patients of the present material is shown in Graph 19. On the basis of this graph it can be stated that adrenals of all sizes are fairly equally divided among all weight groups of the thymus. The smallest



Graph 19. The relationship between the weights of the thymus and the adrenals.

thymuses seem to be accompanied, on the whole, by the smallest adrenals. Hypoplastic adrenals are not present in connection with large thymuses.

The following can be advanced as an explanation of this result:

Large thymuses are usually found in patients who have died of acute diseases, in whom, as is shown by Graph 11, the adrenals also are at their largest. The smallest thymuses again are found in those with diseases of long duration, particularly with patients who die of gastroenteritis (TÄHKÄ 1951), and they also have, as is shown by Graph 12, the smallest adrenals.

As shown by TÄHKÄ elsewhere, the individual variations in thymus weight are exceedingly great. This makes the drawing of conclusions very difficult indeed, and may account for the contradictory results advanced in literature on the relationship between thymus and adrenals.

X. RELATIONSHIP OF THE ADRENALS TO THE THYROID GLAND

HOSKINS (1910), as well as INGLE & HIGGINS (1938) and DEANE & GREEP (1947) found that the adrenal gland is enlarged with increasing activity of the thyroid gland. DEANE & GREEP have shown that hyperthyroidism initially causes cortical hypertrophy, particularly of the zona fasciculata, but signs of exhaustion are often found later. Hypothyroidism, they have found, causes adrenal atrophy.

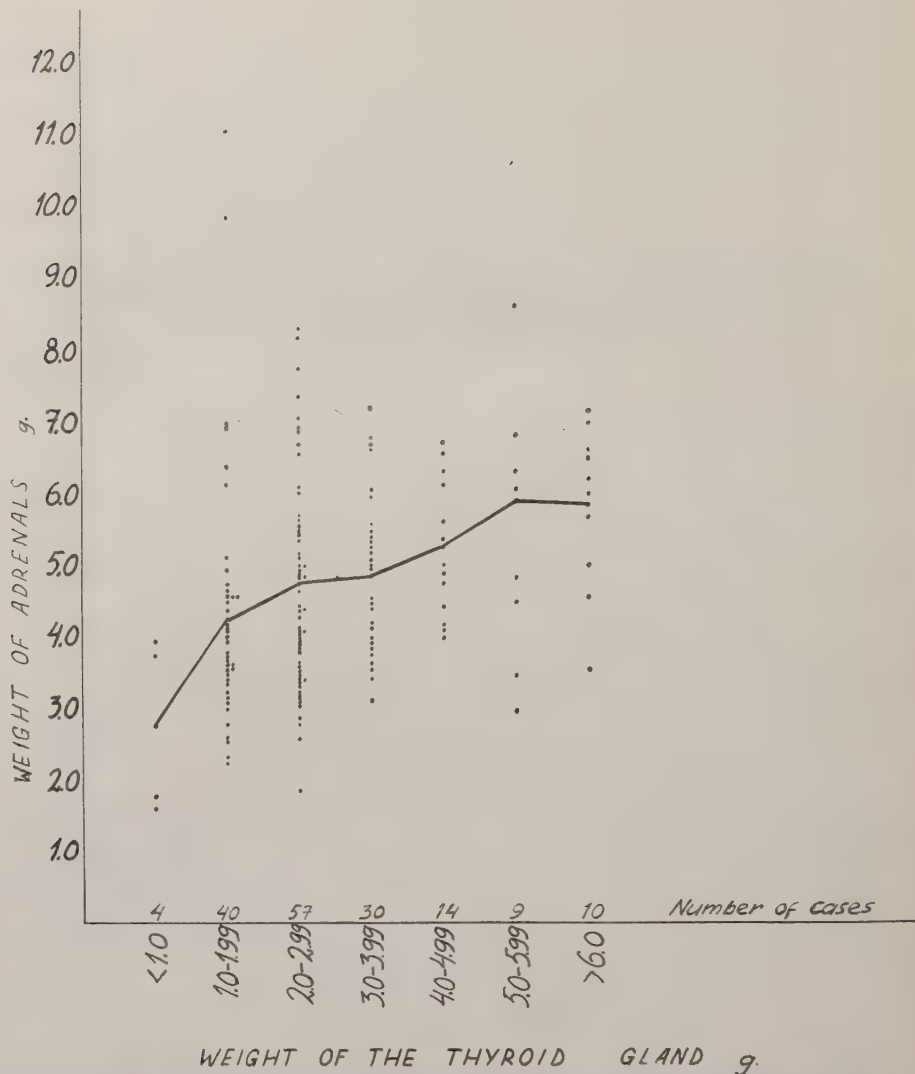
According to SELYE (1946, 1947), the changes produced by the GAS in the thyroid gland are not as distinct as those produced in the adrenal and the thymus. However, during the alarm reaction, signs of reduced thyroid activity are sometimes found, while in counter shock and in the stage of resistance its activities are increased. However, no distinct variations in weight are present.

UOTILA & PEKKARINEN have shown that, with men suffering a rapid death, activation of the thyroid gland can be observed and is expressed both in a rise in weight and in histological changes. In individuals suffering from a disease of longer duration, these phenomena decrease.

Present Investigations

The relationship between the weights of the adrenals and the thyroid gland of the patients of the present material is shown in Graph 20. The curve reveals the average adrenal weight increasing with the increasing weight of the thyroid gland, although exceptions may occur in individual cases.

The thyroid gland weights for the present material are given by TÄHKÄ elsewhere in greater detail. They show that the thyroid gland



Graph 20. The relationship between the weights of the thyroid gland and the adrenals.

is at its largest with patients who have died after a short illness, while with diseases of longer duration its weight decreases somewhat, but the results are not as marked as with the adrenals.

The fact evident from Graph 20, that the weight of the adrenals

and the thyroid gland increase simultaneously, could be explained by attributing the enlargement of the two organs to a common cause. The first cause to suggest itself is the stimulating effect that the tropic hormones of the pituitary exercise on both these organs. However, as the histological structure of the thyroid glands in the present material has not yet been studied, no positive conclusions can be drawn as to the possible parallel fluctuations in the activity of the organs in question.

Cases of Goitre.

UOTILA compared in 1941 the weight and structure of the adrenals and the thyroid glands of the newborn in normal and goitre cases in Finland. In the normal material the average weight of the adrenals was 6.93 g for males and 6.96 g for females, and the corresponding weights of the thyroid gland 2.94 g and 3.33 g. With goitre patients the adrenals weighed, on an average, 8.09 g with males and 8.08 g with females, and the thyroid gland 9.29 g with males and 8.56 g with females. In the histologically most severe cases of goitre the permanent adrenal cortex was unusually small.

Case No	Age	Duration of disease	Diagnosis	Weight of thyroid gland, g	Weight of adrenals, g	Average adrenal weight at same age	Foetal cortex %	Average f.c. % at same age
183/49	20 min.	20 min.	Anencephalus	8.73	7.00	6.50 ± 0.37	84	77
130/49	5 days	5 days	Vitium cordis congenita	6.54	7.15	6.50 ± 0.37	60	65
100/49	11 »	1 day	Septicaemia	7.50	5.62	6.11 ± 0.45	64	55
53/49	28 »	28 days	Haematoma subdurale	6.36	6.15	4.52 ± 0.31	33	27
146/49	1 month	1 month	Vitium cordis congenita	8.02	3.52	4.30 ± 0.36	13	27
354/48	2½ months	1½ months	Gastroenteritis	7.60	4.50	3.51 ± 0.22	18	19
113/49	»	2½ »	Vitium cordis congenita	15.82	4.97	3.51 ± 0.22	12	19
400/48	5½ months	5 months	Tub. miliaris	27.50	6.42	4.64 ± 0.27	11	8
11/49	»	5½ »	Debilitas cong.	19.72	5.95	4.64 ± 0.27	—	8
135/49	»	8 days	Pneumonia	6.57	6.57	4.64 ± 0.27	32	8

Table 29. Cases of congenital goitre.

In the present material 10 patients had goitre, the weight of the thyroid gland exceeding 6 g, considered by LEIDENIUS (1931) and UOTILA (1941) as the goitre limit for Finnish infants. The cases are specified in Table 29.

Table 29 shows that the adrenals generally, in cases of goitre, are larger than the average (exceptions are constituted by Cases 100/49 and 146/49). The average arrived at for the total material is that the adrenal weight for goitre children is 20 % higher than the »normal» weight for the same age. No distinct correlation exists between the size of the goitre and this deviation. Apart from Case 135/49, the amount of the foetal cortex differs fairly little from the mean value for the same age.

This result, hence, is on the same lines as that reported above on the relationship between the weights of thyroid glands of normal size and adrenals.

XI. DISCUSSION

SELYE with his school, SAYERS et al. and numerous other investigators have shown that the most varied range of factors, such as cold, heat, hunger, muscular stresses, poisons, and different infections bring about changes e.g. in the adrenal cortex. In animals, these changes are generally very uniform and conform to relatively firm rules. The adrenal finding in each case is decisively dependent on the kind, intensity and duration of the stress in question.

A study of the adrenal findings in miscellaneous clinical autopsy material gives results that seem very varied. This is in fact evident considering that many simultaneous factors are often at work in the individual cases. Among them may be mentioned the disease proper, the type and intensity of which varies greatly, possible additional diseases, the malnutrition almost regularly present in diseases of long duration in particular, and the strain imposed on the organism by therapeutic measures (e.g. operation), etc. The results are perhaps, in addition, considerably affected by the fact that the starting point in the cases is different. It would seem natural that the reaction of the organism differs with patients where one, on falling ill with his last disease was suffering from malnutrition and had possibly previously experienced a great deal of illness, while the other is a formerly healthy individual in good condition.

Conclusions to be drawn from infant material, are further considerably obscured by the variations in size due to the development of the adrenals, and by the infant's rapid growth at this age.

On the basis of the foregoing it must be stated that hardly any conclusions can be drawn from the adrenal findings observed in individual cases. Instead, the results obtained by age and disease

groups from an extensive material can perhaps be considered as indicative of the course.

When endeavouring to apply the results of animal tests to human material another point to be borne in mind is that reactions in the human organism cannot be immediately assumed as exactly similar to those in animals. As, however, corresponding tests cannot be carried out with men the results of animal tests must be utilised with certain reservations.

On the basis of SELYE's »General Adaptation Syndrome» theory and the results obtained by SAYERS & SAYERS (1948) with test animals, the most usual finding to be expected with the patients of the present material would be large adrenals poor in lipoids. Such, according to SELYE, is the condition of the adrenals at the »stage of exhaustion», and according to SAYERS & SAYERS, when »intense continuous stress has led to death».

With adults ROGERS & WILLIAMS (1948) have often discovered the adrenal findings to be in compliance with the »General Adaptation Syndrome». In Finland, UOTILA & PEKKARINEN have found the same with adults who have died of an acute disease. The adrenal weights of their patients are at their highest in patients who died after a disease of 48 hours, and with the time of reaction extending the size of the adrenals begins to decrease somewhat.

A review of the results obtained from the present material shows that the cases can be divided up, on the basis of adrenal findings, into 3 main groups:

1. With those who died after a disease of short (0—3 and 4—7 days) duration, generally, absolutely and relatively large adrenals, poor in lipoids, are found.

2. In those of the so-called miscellaneous material whose illness has been of lengthy duration, the absolute weight of the adrenals is lower than with the former, differing fairly little, throughout the material, from the normal values. With these patients the relative weight is somewhat increased, and the lipid content of the cortex increases with the duration of disease extending.

3. With patients who died of gastroenteritis of long duration (over 14 days) the absolute weight of the adrenals is distinctly below the normal, and decreases throughout the material with the duration

of disease increasing. The relative weight of the adrenals with these patients increased somewhat. Lipoid content is fairly abundant and increases with extending duration of disease.

The patients of Group 1, by their adrenal findings, can be said to have died at the shock stage of the alarm reaction or at the stage of exhaustion. According to SAYERS & SAYERS, they would correspond to the above-mentioned Type 3, »intense continuous stress sending in death«.

The adrenal finding of the patients in Group 2 corresponds, in the first place, according to SELYE, to adrenals at the resistance stage and to SAYERS & SAYERS Type 2, developing when there is »a very gradual change in the internal or external environment.«

It seems that in these cases, at the time of death, the adrenals are not yet in the exhaustion stage but death has come to the organism in spite of the adrenal cortex still functioning. However, it must be borne in mind that no definite conclusions as to the functioning of the adrenals can be drawn on the basis of their size and lipoid content alone. (ROGERS & WILLIAMS 1947, 1948).

The adrenal finding in Group 3 is reminiscent in the first place of SAYERS & SAYERS's Type 6, in which a small adrenal rich in lipoids is found due to shortage of ACTH developed on the basis of hypopituitarism. Similar adrenals have been described by SELYE in test animals whose hypophysis had been removed a short while previously.

This leads to the assumption that insufficiency of ACTH secretion develops with infants in connection with fatal gastroenteritis of long duration. Possibly the same effect could result in some other disease groups also, but due to the limited range of material it is not demonstrable. One of the reasons why this phenomenon is so marked with diarrhoea patients may be that all the patients that died of chronic diarrhoea had been suffering from malnutrition and had often had to live on insufficient food for several weeks. MULINOS & POMERANTZ (1941) have shown by animal tests that lengthy malnutrition causes adrenal atrophy which, according to MULINOS, POMERANTZ & LOJIKIN (1942), can be cured by transplantation of the hypophysis. In 1946 SELYE found that a diet poor in proteins reduces the secretion of ACTH. UEHLINGER (1948) has found changes in man in the anterior pituitary lobe in chronic hunger conditions. — In prolonged gastro-

enteritis, therefore, two different factors, the disease itself and chronic malnutrition, might have a reducing effect on ACTH incretion.

However, the finding — a small adrenal rich in lipoids — can also be explained by the fact that the disease has damaged the adrenal cortex so severely that it can no longer react to ACTH stimulation. Such adrenals, in gastroenteric patients in particular, may be the direct result of the deleterious influences of malnutrition on the adrenal cortex. Hence, SAYERS (1949) found that, on a diet poor in proteins, rats develop small adrenals rich in lipoids, but that there is no concurrent decrease in ACTH incretion.

MAUN, CAHILL & DAVIS's (1945) statement that a prolonged lack of some amino acids may cause adrenal atrophy, as well as the small adrenals found by JACKSON (1915) in chronic hunger, can perhaps be explained by means of the two effect mechanisms. The same applies e.g. to adrenal atrophy present in connection with chronic malaria, as described by GOLDEN etc.

Whether the established adrenal atrophy is a consequence of the lack of ACTH or of direct adrenal lesion is a question that cannot be solved on the basis of the present investigations. Its solution would require experiments in adrenal function.

KERPEL-FRONIUS & VARGA (1949) found general organic atrophy in patients who died of prolonged gastroenteritis. Hence, the suggestion presents itself that the small adrenals found in the present investigation might be a part symptom of this general atrophy of the organs, which again might be due to the fact that the organ governing many of the functions of the organism, the pituitary gland, might be inadequate in its functioning. This theory is supported e.g. by the fact that Simmonds' disease can develop in connection with chronic infectious diseases (HILDEBRAND & RYNEARSON 1943, SELYE 1950). In addition, the weakening of genital functions often encountered in connection with chronic diseases may also be of hypophyseal origin (BERNTH & HAGENS 1944, GUGGISBERG 1946, etc.). The same explanation can perhaps be advanced for ELO's (1945) observation that patients who have died of tuberculosis often display atrophy of the ovaries and of the mucous membranes of the uterus.

To sum up, it can be stated that it seems obvious that the adrenals of infants and young children, in diseases leading to a rapid death, conform in their reaction with the principles of the GAS. In prolonged

cases the adrenal finding corresponds, in the first place, to an organ at the stage of resistance. An exception is constituted by the patients who die of gastroenteritis, who develop adrenal atrophy which can be explained firstly as a part phenomenon of a general exhaustion of the organism probably brought on by insufficiency in the pituitary function.

XII. SUMMARY

The adrenals were removed from 311 infants who had died of different diseases. They were weighed and stained with Delafield's haematoxylin and eosin; Scarlet-red and Liebermann—Burchard—Schultze stainings were made of the frozen sections, and some of them were inspected in polarized light. Variations in the size and lipid content of the adrenals and the involution of the foetal cortex were observed by age, sex, birth weight, duration of disease and type of disease. In addition, the thymus was removed from 309 patients and the thyroid gland from 244 patients. The weights of these organs were compared with the weights of the adrenals.

The results show the following:

1. The absolute weight of the adrenals decreases from birth to the age of 3 months from 6.50→3.51 g. The weight then rises slowly, without, however, attaining the weight of the newborn by the age of two years. With premature births the absolute values are lower, but the trend of development otherwise is similar.

2. The relative weight of the adrenals decreases continuously from 0 to 2 years. The values are roughly of the same range with full-term infants and premature births.

3. The adrenals grow considerably towards the end of pregnancy.

4. No difference is found between the weights of the adrenals of male and female infants.

5. The considerable decrease of the adrenals in the earliest months of life is probably largely due to the involution of the foetal cortex. At birth the foetal cortex is found to constitute 73 %, and with premature births 77 %, of the whole adrenal cortex. Up to the age of 21 days the foetal cortex decreases fairly regularly, and the involution continues even after that, but the individual variations

are considerable. The connective tissue capsule surrounding the medulla is visible in practically all the patients of the material.

6. In cases where the foetal cortex percentage differs considerably one way or another from the average, no mutual correlation can be demonstrated as regards the type of disease, duration of disease or size of the adrenals.

7. The largest adrenals, on an average, are found with patients who have died of an illness of short duration (0—3 and 4—7 days).

8. With patients who have died of prolonged diarrhoea, the adrenals decrease continuously with extending duration of disease, attaining distinctly sub-normal values. In the so-called miscellaneous material, consisting of other fullterm patients over 14 days of age, the adrenal weight in prolonged cases is more or less unchanged, varying but little to either side of the »normal» values of the material.

9. The relative weights of the adrenals, throughout the material, are higher than normal. However, they do not rise as much as is presupposed e.g. by the loss in weight of chronic gastroenteric patients.

10. Results obtained as regards the lipid contents of the adrenals, with the three histological determination methods employed, correspond fairly closely. In 19 cases, in addition, it has been possible to compare the results with chemical lipid determinations. It seems that the chemical and histological lipid contents are fairly similar.

11. The average lipid content, by all methods, is smaller in the gastroenteric, premature birth and newborn materials than with patients who have died of other diseases.

12. The results obtained from the total material and by all methods of staining seems to indicate that in patients who have died rapidly the adrenals are poor in lipids, and that the lipid content increases with prolonged duration of disease. This fact is mathematically demonstrable in the diarrhoea material only, from results obtained by cholesterol staining.

13. No distinct regularity is present in the variations in the lipid content of the different zones of the adrenal cortex in the different disease and duration of disease groups.

14. Furthermore, the adrenals have been studied separately in certain disease groups in which, according to the literature, changes are often found. With the patients of the present material who died

of cerebral deformity, congenital heart malformation, pyloric stenosis or erythroblastosis foetalis, adrenals differing greatly from the average cannot be demonstrated. A fairly extensive haemorrhage in the adrenal cortex was found with three patients, but with none of them was this the cause of death, at least not the only cause.

15. No distinct correlation can be shown between the weights of the thymus and the adrenals.

16. The relationship between the weights of the thyroid gland and the adrenals evidences that the average adrenal weight rises as the weight of the thyroid gland increases. Adrenals exceeding the average by some 20 % are found in goitre patients.

17. The many factors affecting the adrenal changes are discussed, with the inference that they make the drawing of conclusions considerably more difficult.

18. It is found that the adrenal finding with children who have died after a short duration of disease appears to correspond in the first place to the shock or exhaustion stage of Selye's »General Adaptation Syndrome». In the miscellaneous material, again, the adrenals, in the first place, seem to be at the »stage of resistance». The small adrenals, rich in lipoids, found in connection with chronic diarrhoeas, must be understood primarily as a result of the lack of ACTH brought about by the disease.

XIII. REFERENCES

- ADAMS, E. and BAXTER, M.: Arch. Path. 1948: 48: 13.
- ADDISON, T.: Quoted by Goldzieher 1946.
- ALLIBONE, K. J., BAAR, H. S. and CANT, W. H. P.: Arch. Dis. Childh. 1947: 22: 210.
- ARMSTRONG, H. G. and HEIM, J. W.: J. Aviat. Med. 1938: 9: 92.
- ATKINSON, F. R. B.: Brit. J. Childr. Dis. 1938: 35: 96.
- BABES, V.: C.r. Soc. Biol. 1908: 2: 235.
- BAMATTER, F.: Jb. Kinderhk. 1934: 142: 129.
- BARTA, L.: Ann. Paediatr. 1948: 171: 158.
- BENNER, M. C.: Amer. J. Path. 1940: 16: 787.
- BENNETT, H. S.: Amer. J. Anat. 1940: 67: 151.
- BERNTH OG HAGENS: Medicinsk Kompendium. 4. udgave. Store Nordiske Videnskapsboghandel. København 1944.
- BEUMER, H.: Mschr. Kinderhk. 1921: 19: 409.
- BLACKMAN, JR, S. S.: Bull. Hopkins Hosp. 1946: 78: 180.
- BLUMENSAAT, C.: Virchows Arch. 1929: 271: 639.
- BORBERG, N. C.: Skand. Arch. Physiol. 1915: 32: 287.
- BOSCOTT, R. J, MANDL, A. M., DANIELLI, J. F. and SHOPPEE, C. W.: Nature (London) 1948: 162: 572.
- BOURNE, G. H.: The Mammalian Adrenal Gland. Oxford University Press 1949.
- BOYD, W.: Textbook of Pathology, 4th edition. London. Henry Kimpton 1943.
- BRUN: Bibl. Laeg. 1939—40: 131: 197.
- CARLGREN, L-E.: Acta Paediatr. 1949: 38: 71.
- CASTALDI, L. and VANNUCCI, D.: Quoted by Krogman: Growth of man. Tabulae Biologicae 1941 vol. 20.
- CHAUFFARD, A., LAROCHE, G. and GRIGAUT, A.: C.r. Soc. Biol. 1914: 1: 529.
- CH'INK, Y. and HSUCH, C. S.: Zbl. Kinderhk. 1941: 38: 377.
- CLATWORTHY, H. W. and ANDERSON, R. G.: Amer. J. Dis. Childr. 1944: 67: 167.
- CRAMÉR, H.: Sannolikhets Kalkylen. — Almqvist & Wicksell, Uppsala 1949.
- DALTON, A. J. and SELVE, H.: Anat. Rec. Suppl. 1938: 72: 48.
- DARROW, D. C.: J. Pediatr. 1946: 28: 515.
- » PRATT, E. C., FLETT, Jr, J., GAMBLE, A. H. and WIESE, H. F.: Pediatrics 1949: 3: 129.
- » and SARASON, E. L.: J. clin. Invest. 1944: 23: 11.

- DEANE, H. W. and GREEP, R. O.: *Amer. J. Anat.* 1946: 79: 117.
 —»— and —»— *Endocrinology* 1947: 41: 243.
 —»— and MCKIBBIN, J. M.: *Endocrinology* 1946: 38: 385.
 —»— and SHAW, J. H.: *J. Nutrit.* 1947: 34: 1.
 —»— —»— and GREEP, R. O.: *Endocrinology* 1948: 43: 133.
 DEMPSEY, E. W. and WISLOCKI, G. B.: *Physiol. Rev.* 1946: 26: 1.
 DEUCHER, G. W.: *Arch. klin. Chir.* 1923: 125: 578.
 DOSNE, C. and DALTON, A. J.: *Anat. Rec.* 1941: 80: 211.
 DUGUID, J. B. and MILLS, J.: *J. Path. a. Bact.* 1928: 31: 721.
 EKHOLM, E. and NIEMINEVA, K.: *Acta Paediatr.* 1950: 39: 67.
 ELLIOT, T. R. and ARMOUR, R. G.: *J. Path. a. Bact.* 1911: 15: 481.
 —»— and TUCKETT, I.: *J. Physiol.* 1906: 34: 332.
 ELO, R.: Thesis, Helsinki 1945. Über den Einfluss der Lungentuberkulose auf die Menstruation.
 EUSTACHIUS, B.: Quoted by Bourne 1949.
 FANCONI, G. and LANDOLT, R. F.: *Helvet. paediatr. Acta* 1949: 4: 15.
 —»— —»— *Ibid.* 1949: 4: 22.
 FEULGEN, R. and VOIT, K.: *Pflügers Arch.* 1924: 206: 389.
 FEX, J.: *Biochem. Z.* 1920: 104: 82.
 FLEXNER, L. B. and GROLLMAN, A.: *Anat. Rec.* 1939: 75: 207.
 FORSELL, P.: *Ann. M.d. Fenn.* 1947: 36: 247.
 —»— *Ibid.* 1948: 37: 16.
 FRIEDRICHSEN, C.: *Jb. Kinderhk.* 1918: 87: 109.
 GAMBLE, J. L.: *Extracellular Fluid.* — Harvard University Press, Cambridge, Mass. 1947.
 GOLDEN, A.: *Feder. Proc.* 1948: 7: 271.
 GOLDZIEHER, M. A.: *Wien, klin. Wschr.* 1910: 22: 809.
 —»— *Endocrinology* 1934: 18: 179.
 —»— *The Adrenal Glands in Health and Disease.* Philadelphia, F. A. Davis Co 1946.
 —»— and GORDON, M. B.: *Klin. Wschr.* 1930: 12: 270.
 —»— —»— *Endocrinology* 1932: 16: 165.
 GRAHAM, G. S.: *J. med. Res.* 1916: 34: 241.
 GROLLMAN, A.: *The Adrenals.* — The Williams & Wilkins Co. Baltimore 1936.
 GUGGISBERG, H.: *Lehrbuch der Gynäkologie.* — Verlag von S. Karger in Basel 1946.
 HALLMAN, H. F.: *Endocrinology* 1944: 34: 187.
 HALLMAN, N.: To be published.
 —»— and AHVENAINEN, E. K.: *Ann. M.d. Fenn.* 1950: Suppl. 7.
 —»— and TÄHKÄ, H.: *Ann. M.d. Fenn.* 1950: 39: 95.
 HAMMILL, S. M.: *Arch. Pediatr.* 1901: 18: 161.
 HARTMAN, F. A. and BROWNELL, K. A.: *The Adrenal Gland.* — London, Henry Kimpton 1949.
 HASNER, E.: *Acta chir. Scand.* 1949: 92: 51.

- HENCH, PH. S., KENDALL, E. C., SLOCUMB, C. H. and POLLEY, H. F.: Proc. Staff. Meet. Mayo Clin. 1949: 24: 181.
- HENI, F.: Z. exper. Med. 1941: 108: 427.
- HERMANN, O.: M. chr. Kinderhk. 1940: 82: 76.
- HETT, J.: Z. mikrosk.-anat. Forsch. 1925: 3: 179.
- HILDEBRAND, A. G. and RYNEARSON, E. H.: Arch. int. Med. 1943: 71: 262.
- HOSKINS, R. G.: J. A. M. A. 1910: 55: 1724.
- HOWARD, E.: Anat. Rec. 1940: 77: 181.
- HUEBSCHMANN: Zbl. Path. 1921: 31: 568.
- INGLE, D. J. and HIGGINS, G. M.: Endocrinology 1938: 23: 419.
- JACKSON, C. M.: Amer. J. Anat. 1909: 9: 119.
- — — Ibid. 1915: 18: 75.
- — — Ibid. 1919: 25: 221.
- JAFFÉ, H. L.: J. exper. Med. 1924: 40: 325.
- — — Ibid. 1924: 40: 619.
- JAUDON, J. C.: J. Pediatr. 1946: 28: 737.
- KAPPERT, A.: Helvet. med. Acta 1947: 14: 5.
- KARWICKA, M. D. Beitr. path. Anat. 1911: 50: 437.
- KAWAMURA, R.: Die Cholesteriesterverfettung. Jena, Gustav Fischer 1911.
- KAY, W. W. and WHITEHEAD, R.: J. Path. a. Bact. 1935: 41: 293.
- KEENE, M. F. L. and HEWER, E. E.: J. Anat. 1927: 61: 302.
- KEILMANN, K.: Z. Kinderhk. 1923: 35: 25.
- KELLNER, B.: Zbl. Path. 1933: 57: 407.
- KERN, H.: Dtsch. med. Wschr. 1911: 21: 971.
- KERPEL-FRONIUS, E. and VARGA, F.: Pediatrics 1949: 4: 301.
- KNOUFF, R. A., BROWN, J. B. and SCHNEIDER, B. M.: Anat. Rec. 1941: 79: 17.
- KOLMER, W.: Arch. mikrosk. Anat. 1918: 91: 1.
- Z. LAGE, H.: M. chr. Kinderhk. 1940: 82: 91.
- LANDAU, M.: Dtsch. med. Wschr. 1913: 7: 300.
- — — Ibid. 1913: 12: 546.
- LEIDENIUS, L.: Acta Soc. Medic. fenn. Duodecim. Ser. B. Tom. XVI, 1931.
- LEWIS, R. W. and PAPPENHEIMER, A. M.: J. med. Res. 1916: 34: 81.
- LIEBEGOTT, G.: Beitr. path. Anat. 1944: 109: 93.
- LITTLE, E. G.: Quoted by Goldzieher 1946.
- LOESCHKE, E.: Münch. med. Wschr. 1910: 57: 48.
- LOMER, R.: Virchows Arch. 1884: 98: 366.
- LONG, C. N. H.: Recent Progress in Hormone Research, I: 99: 1947.
- MACLEAN, A.: J. Hyg. 1937: 37: 345.
- MACLEAN, A. B., SULLIVAN, R. C. and ZWEMER, R. L.: Amer. J. Dis. Childr. 1932: 43: 1277.
- MARINE, D., MANLEY, O. T. and BAUMANN, E. J.: J. Exper. Med. 1924: 40: 429.
- MATERNA, A. and JANUSCHKE, E.: Virchows Arch. 1927: 263: 537.
- MATTI, H.: Mitt. Grenzgeb. Med. u. Chir. 1912: 24.
- MAUN, M. E., CAHILL, W. H. and DAVIS, R. M.: Arch. Path. 1945: 39: 294.
- — — — — Ibid. 1945: 40: 173.

- MCNEILL, M.: *Ulster med. J.* 1947: 16: 41.
- MENTEN, M. L. and SMITH, M. P.: *Amer. J. Dis. Childr.* 1936: 52: 54.
- MEYER, R.: *Virchows Arch.* 1912: 210: 158.
- MOON, V. H.: Quoted by Selye 1950.
- MULINOS, M. G. and POMERANTZ, L.: *Amer. J. Physiol.* 1941: 132: 368.
- MULINOS, M. G., POMERANTZ, L. and LOJIKIN, M. E.: *Endocrinology* 1942: 31: 276.
- NEYMANN, N.: *Arch. Gynäk.* 1939: 168: 79.
- NICHOLS, J. and HILL, Ch.: *Arch. Path.* 1948: 45: 717.
- OPPENHEIM, R. and LOEPER, M.: *C.r. Soc. Biol.* 1901: 53: 318.
- — — *Ibid.* 1903: 55: 330.
- PFEIFFER, H.: *Z. exper. Med.* 1919: 10: 1.
- PIRIE, G. R., TOR, M. B. and LOND, M. R. C.: *Lancet* 1919: 2: 513.
- PLECNICK, J.: *Arch. mikrosk. Anat. u. Entw. gesch.* 1902: 60: 414.
- RANTASALO, I.: Lecture delivered at the meeting of Finnish Pediatrics Society on 6. 5. 1950.
- RICH, A. R.: *Bull. Hopkins Hosp.* 1944: 74: 1.
- ROGERS, PH. V. and RICHTER, C. P.: *Endocrinology* 1948: 42: 46.
- ROGERS, W. F. and WILLIAMS, R. H.: *Arch. Path.* 1947: 44: 126.
- — — *Ibid.* 1948: 46: 451.
- ROMEIS, B.: *Taschenbuch der mikroskopischen Technik*, 14 Auflage München und Berlin 1943.
- ROMINGER, E.: *Ann. Paediatr.* 1948: 171: 344.
- ROSENBAUM, P.: *Z. Kinderhk.* 1931: 51: 70.
- SARASON, E. L.: *Arch. int. Med.* 1943: 71: 702.
- — — *Arch. Path.* 1943: 35: 373.
- SAYERS, G.: *J. Clin. Endocrinol.* 1949: 9: 656.
- — — and SAYERS, M. A.: *Recent Progress in Hormone Research II*: 81: 1948.
- — — Sayers, M. A., FRY, E. G., WHITE, A. and LONG, C. N. H.: *Yale J. Biol. a. Med.* 1943—44: 16: 361.
- SCAMMON, R. E.: *Proc. Soc. exper. Biol. a. Med.* 1926: 23: 809.
- SCHEEL, O.: *Virchows Arch.* 1908: 192: 494.
- SCHILF, F.: *Z. Konstit. lehre* 1922: 8: 507.
- SCHOENHEIMER and SPERRY, W. M.: *J. biol. Chem.* 1934: 106: 745.
- SCHRIDDE, H.: L. Aschoff: *Pathologische Anatomie*, 2. Aufl. Gustav Fischer, Jena 1911.
- SELYE, H.: *Endocrinology* 1937: 21: 347.
- — — *J. Clin. Endocrinol.* 1946: 6: 117.
- — — *Textbook of Endocrinology*, Second Edition, Acta Endocrinologica Inc. Montreal, Canada 1949.
- — — *The Physiology and Pathology of Exposure to STRESS*. Acta, Inc. Medical Publishers. Montreal, Canada 1950.
- SIKL, H.: *J. Path. a. Bact.* 1948: 60: 323.
- SIMMONS, K. and TODD, T. W.: *Growth* 1938: 2: 93.
- SPOLVERINI, M.: *Arch. Kinderhk.* 1916: 65: 130.

- STARKEL, S. and WEGRZYŃSKI, L.: Arch. Anat. u. Entw. gesch. 1910: 214.
- STEPHANI, E.: Jb. Kinderhk. 1923: 101: 201.
- SWINYARD, C. A.: Anat. Rec. 1940: 76: 69.
- »— Ibid. 1943: 87: 141.
- V. SZASZ, A.: Mschr. Kinderhk. 1939: 79: 332.
- »— Ibid. 1941: 88: 307.
- THADDEA, S.: Erg. inn. Med. 1938: 54: 753.
- THOMAS, E.: Beitr. path. Anat. 1911: 50: 283.
- TOBECK, A.: Virchows Arch. 1928: 267: 690.
- TÁHKÄ, H.: To be published in Acta Paediatr.
- »— —»— —»—
- UEHLINGER, E.: Quoted by Yearbook of Endocrinology, Metabolism and Nutrition. 1948: 29.
- »— Quoted by Selye 1950.
- UOTILA, U. U.: Duodecim 1940, Suppl. 2.
- »— Acta Soc. Medic. fenn. Duodecim. Ser. B. Tom. XXX fasc. 3: 50, 1941.
- »— and PEKKARINEN, A.: Acta endocrinol. 1951: 6: 23.
- VERZÁR, F.: Lehrbuch der Inneren Sekretion. Liestal 1948.
- VIRCHOW, R.: Arch. path. Anat. 1857: 12: 481.
- WATERHOUSE, R.: Lancet 1911: 1: 577.
- WELTMANN, O.: Beitr. path. Anat. 1913: 56: 278.
- ZANDER, R.: Beitr. path. Anat. 1890: 7: 439.
- ZWEMER, R. L.: Amer. J. Path. 1936: 12: 107.

